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INVOLVEMENT OF THE ILEUM IN CHRONIC ULCERATIVE COLITIS*

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THE fact that extension of the inflammatory process to the terminal portion of the ileum occurs in patients with chronic ulcerative colitis is fairly well known, but it has not received sufficient emphasis. The ileocecal valve does not limit the progress of the lesions of ulcerative colitis into the terminal part of the ileum any more than it prevents secondary involvement of the colon from the ileum in cases of regional enteritis. The type of chronic ulcerative colitis that begins in the rectum and spreads orad may in many cases extend into the terminal part of the ileum; it may continue for great distances up the ileum, and in a few cases it may involve even the jejunum.

It is a well recognized and established fact that so-called regional or segmental or right-sided colitis is associated with a high incidence of ileal involvement. Crohn, Garlock and Yarnis[1] reported the incidence of involvement of the ileum in these cases to be as high as 8 per cent. Bargen and Weber[2] likewise cited a high incidence of ileal involvement in these cases — namely, 6.3 per cent. It must be kept in mind that this type of colitis comprises only a very small percentage of all cases of chronic ulcerative colitis. In this paper we are not concerned with the segmental type of colitis; furthermore, we have excluded from this study specific types of inflammation of the ileocecal coil such as those caused by tuberculosis, amebiasis and actinomycosis. We have therefore included only cases of diffuse chronic ulcerative colitis of the thromboulcerative variety — the streptococcal type described by Bargen and Weber[2] — that characteristically begin in the rectal segment and spread cephalad and, in time, involve the whole colon. It is this variety that makes up the vast majority of the cases of ulcerative colitis encountered clinically.

To restrict this study to ileums that had been diseased secondary to the type of chronic ulcerative colitis defined above, only cases in which the lesions showed the typical and characteristic proctoscopic and roentgenologic features of this form of colitis were selected. In all the cases the first signs of inflammation were related to the rectum and distal segments of the large bowel as determined on the basis of proctoscopic findings. The shortening and deformity of the entire colon consistent with this type of colitis was noted roentgenologically in all the cases in which studies were made with the aid of barium enemas. These cases were analyzed to determine the incidence, extent, pathological nature, clinical significance and prognosis of ileal involvement in cases of chronic ulcerative colitis.

MATERIAL AND METHODS

This paper comprises a complete pathological study of 23 post-mortem specimens of bowel in cases of diffuse chronic ulcerative colitis in which the ileum was involved and of 6 surgical specimens that included a small segment of the involved terminal part of the ileum, which had been resected along with part or all of the diseased colon. The cases were encountered at the Mayo Clinic from 1935 through 1946.

The clinical records were carefully reviewed to ensure that the cases studied fell into the category already referred to. For this, reliance was placed on the proctoscopic and roentgenologic data. All cases not conforming to these criteria were purposely omitted.

All the gross specimens, surgical and post mortem, utilized in this study had been preserved in 10 per cent formalin at the Mayo Clinic Museum. Each gross specimen was inspected to determine the nature and extent of the gross involvement of the ileum. Multiple blocks of tissue were removed from various areas of ileal involvement. These blocks were placed in a fresh 10 per cent solu-

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tion of formalin, sectioned on a freezing microtome, stained with hematoxylin and eosin and mounted permanently on glass slides. The slides were studied carefully for the type and extent of ulceration and inflammatory invasion in each of the coats of the ileum.

Since the clinical entity of regional enteritis was not described until 1932 by Crohn, Ginzburg and Oppenheimer[3] and since ileal involvement was not to be confused with regional enteritis, no cases encountered before 1935 were included in this study.

Historical Review

Chronic ulcerative colitis probably was first described in 1875 by Wilks and Moxon[4] in their lectures on pathologic anatomy. This report makes no mention of whether there was simultaneous involvement of the small intestine. The first record of the recognition of this disease as a pathologic entity was made when Allchin,[5] in 1885, exhibited before the London Pathological Society a post-mortem specimen illustrating the features of chronic ulcerative colitis. Allchin mentioned the small intestine only to state that it was perfectly normal. In 1888 White[6] reported a series of cases from Guy's Hospital in London. He presented a detailed description of the lesions encountered in 11 cases of chronic ulcerative colitis of unknown etiology, and it was noteworthy that he showed in 5 of these cases a similar involvement of the ileum of varying degrees. Evidently, since his first case report in 1885, Allchin had encountered cases of chronic ulcerative colitis with some ileal involvement, because writing again in 1909 he[7] stated that this disease involved the entire bowel from cecum to anus, occasionally even extending into the ileum. In 1915, Hewitt and Howard,[8] in noting the relation of polyps of the colon to the inflammatory process, described at length the autopsy findings in 2 cases of chronic ulcerative colitis and polyposis. In 1 of these cases definite ulcerative disease in the lower two thirds of the ileum as well as in the colon was described. In 1919 Logan,[9] of this clinic, presented a statistical study of 117 cases of chronic ulcerative colitis. In 3 of the 13 cases in this group in which autopsy was performed, fresh ulcers in the lower portion of the ileum were noted. Smith,[10] in 1925, presented an excellent, though brief, pathological description of this disease and stated that the ileum was practically never involved in the nonspecific inflammatory process that affected the colon. He offered as a reason for the relative infrequency of involvement of the terminal portion of the ileum the acid reaction in this part of the ileum, which he believed probably protected it from ulceration. From 1926 to 1932 many authors writing about the pathology of chronic ulcerative colitis did not mention ileal involvement. In 1932 Rankin, Bargen and Buie[11] said that only late in its course, after repeated severe exacerbations, did the disease occasionally pass the ileocecal valve to involve the terminal portion of the ileum. They added that the process in the ileum was less severe or advanced than that in the colon.

Incidence

McKittrick and Miller,[12] in 1935, placed the incidence of ileal involvement in chronic ulcerative colitis at 1.3 per cent in their cases. In 1941 Cave[13] reported that in 8 out of 81 cases (10 per cent) of chronic ulcerative colitis there was involvement of the ileum. McMillan,[14] writing in 1942, declared that nearly 25 per cent of the cases of diffuse ulcerative colitis were associated with "backwash" into the terminal portion of the ileum. He also commented on the rarity of hyperplastic and granulomatous types of inflammatory reactions in the ileum. In 1944, in describing his technic for ileostomy, Cattell[15] observed that he had found involvement of the ileum in approximately a sixth of his operative cases; he cautioned against making a stoma in an ileum that was involved in an inflammatory process. In the same year Crandon, Kinney and Walker[16] reviewed reports of 16,500 consecutive autopsies to determine the frequency of ileal involvement. They found 44 cases in which chronic ulcerative colitis was considered the cause of death. In 17 of these cases, or 39 per cent, there was simultaneous involvement of the small intestine. Dennis,[17] in 1945, probably found the highest incidence (33 per cent) of ileal involvement in this disease from his observations at the time of operation. Before proceeding to do an ileostomy, he routinely resected a small segment of intestine for immediate gross pathological study to rule out ulcerative ileitis at this level. He found the presence of diseased bowel at the site of ileostomy to predispose to the development of postoperative diarrhea and a fecal fistula. Thus, the incidence of ileal involvement reported in the literature varied from 1.3 to 39 per cent.

Pathology

Except for the occasional mention of ileal lesions in chronic ulcerative colitis, the medical literature reveals a complete lack of pathological data on this subject. As far as could be ascertained, a few authors have described the gross appearance of involved intestine, but no one had made a combined and detailed gross and microscopical study of the intestine in these cases.

Most authors, including Baird,[18] Bargen,[19] Cave,[20] Colp,[21] Crohn and Rosenak[22] and McMillan,[14] who have observed ileal involvement in chronic ulcerative colitis apparently believed that it merely represented a retrograde extension of the inflammatory process through the ileocecal valve, a sort of "backwash" into the terminal portion of the ileum. Crohn and Rosenak,[22] in describing the gross pathological appearance of the ileum in chronic

ulcerative colitis, contended that the disease in the ileum is a destructive and denuding process as it is in the colon. They differentiated the process grossly from that seen in primary ileitis in that the ileum failed to present the hyperplastic, stenotic and granulomatous appearance that is characteristic of primary ileitis but showed only the flat superficial ulcerations characteristic of the colon in chronic ulcerative colitis. To show how chronic ulcerative colitis can involve the ileum they described a striking example in which the ulcerations caused by colitis involved the ileum in a previously made ileosigmoidal stoma, with subsequent perforations of the ileum and generalized peritonitis. Mallory[23] described a case, encountered at autopsy, of chronic ulcerative colitis with ileal involvement and brought up the question of the pathologist's ability to differentiate, on anatomic and histologic grounds, the ileum in chronic ulcerative colitis from the ileum in regional ileitis. He expressed the belief that these two different clinical entities can be definitely distinguished from each other on the basis of the pathological appearance of the ileum.

Mallory[24] described the histologic picture of regional ileitis, referring to the characteristic and typical pseudotubercle formation, the marked inflammatory invasion of the deeper layers of the bowel wall and the tendency to fistula formation; in contrast, he commented on the absence of these features in the ileum involved as a result of extension of chronic ulcerative colitis. Ulceration and denudation seemed to these authors to be the prominent gross pathological features in the ileum involved as a result of extension of chronic ulcerative colitis.

Although Cave[20] recognized the probability that ileal involvement in chronic ulcerative colitis occurs as a result of a continuation or spread of the process backward through the ileocecal valve, he mentioned the fact that in 7 of the 80 patients on whom he operated primarily for ulcerative colitis, he found inflammatory lesions in the small intestine resembling those of regional enteritis.

Few writers have discussed the complications of ileal involvement in chronic ulcerative colitis. Castleman[25] reported a case of chronic ulcerative colitis in which perforation of the ileum occurred. The ileum was remarkably hemorrhagic and thin, and when it was opened there were numerous ulcers measuring 1 to 2 cm. in diameter, 3 of which had perforated. These ulcerations had appeared proximal to a previously made ileal stoma. Crandon, Kinney and Walker[16] reported 2 cases of ileal perforations proximal to ileal stomas in chronic ulcerative colitis; the lesions in these ileums were identical with those found in the colon in chronic ulcerative colitis. They presented supportive evidence that the process had existed, at the time of operation, in the ileum above the site elected for enterostomy. These authors also reported a remarkably high incidence of perforation of the small bowel in their cases. Perforation occurred in lesions of the ileum in 4 of the 17 cases in which there was involvement, an incidence of 24 per cent. This was even higher than the incidence of perforation in the colon itself, which was 16 per cent.

Jankelson, McClure and Sweetsir,[26] in 1945, reported 11 cases of acute perforation of the bowel in chronic ulcerative colitis, the mortality rate from the complication being 100 per cent. In 4 of these 11 cases, or 36 per cent, the perforation was in the lower part of the ileum. In the remaining 7 cases some segment of the colon was involved. Corbett,[27] writing at the same time, in discussing the complications of ileostomy stated that abscesses and fistulas into adjacent structures and the abdominal wall often formed proximal to the stoma as a result of perforating lesions in the diseased ileum in chronic ulcerative colitis. He reported 2 cases, in 1 of which death occurred as a result of this complication.

Mayo Clinic Series

Incidence of Ileal Involvement

In the selection of the 29 cases that are the subject of this study, the data on 103 cases of diffuse thromboulcerative colitis were reviewed. All these cases satisfied the proctoscopic and roentgenologic criteria for this study, as outlined above. The data in 81 of these 103 cases were based on post-mortem observation; in 23 of the 81 cases, or 28 per cent, there was definite evidence of ileal involvement. The data in 22 of the 103 cases were based on surgical findings; 6 of the surgically resected colons in these 22 cases showed involvement of the attached ileal segment, an incidence of 27 per cent. The incidence of ileal involvement in the 103 cases of chronic ulcerative colitis was 28 per cent.

Incidence by Age and Sex

Of the 29 patients, 15, or 52 per cent, were males. Twenty-four, or 83 per cent, of the patients were in the first three decades of life, and 5, or 17 per cent, were in the fourth decade. The youngest subject was thirteen years old, and the oldest was forty-seven.

Nature of Disease in Ileum

Gross findings. An analysis of the pathological features of the 29 specimens that formed the basis for this study showed that the ileum was affected by one of two inflammatory processes. In 22 cases the terminal portion of the ileum presented a gross pathological picture similar to that found in the corresponding colon — that is, the ileal segment was completely and diffusely involved in ulcerative changes (Fig. 1, 2 and 3). In the other 7 cases separate ulcers appeared intermittently in the ileum, the intervening portions of small intestine remaining essentially normal (Fig. 4). In all 29 cases the in-

flammatory reaction was much milder and far less advanced than that seen in the diseased colon. This is in agreement with previous observations made by Rankin, Bargen and Buie.[11]

The severer degree of inflammatory changes in the ileum was found in the 22 cases in which the terminal part of the ileum presented to the naked eye the same gross appearance as that found in the chronically diseased colon. The ulceration of the mucosa of the ileum in these cases was so marked that there was almost complete loss of the mucosa except for a few polypoid islands of mucosa. There was complete loss of the transverse folds and villi of the ileum. The inflammatory process represented a direct continuation of the changes in the colon through the ileocecal valve, characterized by long lines of longitudinally running ulcerations. The ulcers were irregular and exhibited a great deal of undermining and coalescing. The gross features in these cases resembled greatly those of polyposis cystica of Virchow, which also is characteristically manifest in the colon in the same cases.

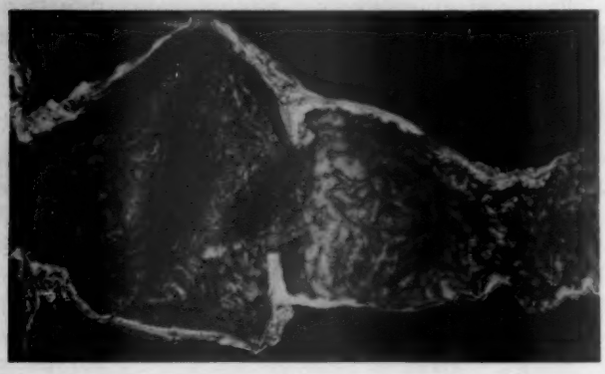

FIGURE 1. *Diffuse Thromboulcerative Colitis Affecting the Cecum, with Extension through the Ileocecal Valve to Involve the Terminal Portion of the Ileum.*

Note the diffusely ulcerated and denuded mucosal surface of the ileum and the absence of any appreciable thickening of the wall.

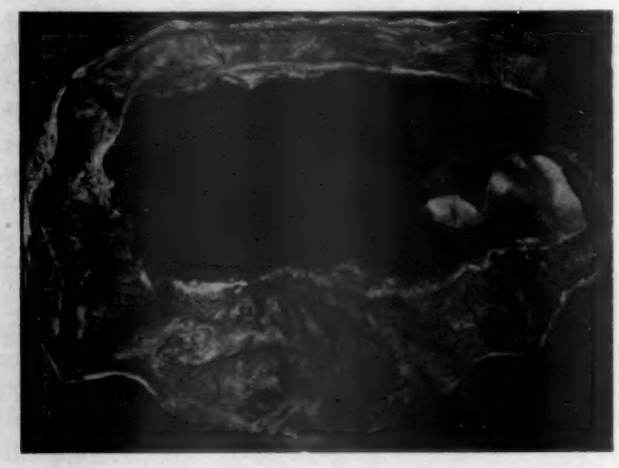

FIGURE 2. *Diffuse Thromboulcerative Colitis in the Colon, with Some Extension into the Terminal Part of the Ileum.*

The terminal segment is diffusely ulcerated.

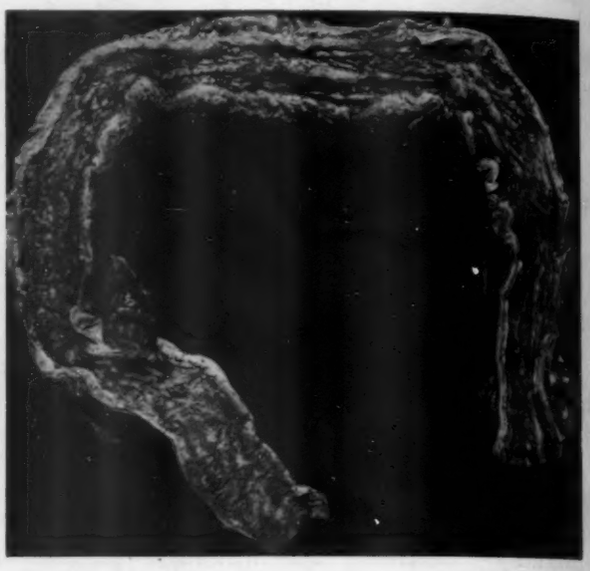

FIGURE 3. *Diffuse Thromboulcerative Colitis of the Entire Colon, with Extension into the Terminal Portion of the Ileum.*

In the other 7 cases the disease was not quite so denuding or destructive, although ulcerative changes in the ileum occurred. These specimens did not reveal the involvement as a diffuse process continuing back from the colon but showed multiple ulcers that had a scattered or patchy distribution, leaving variable amounts of relatively normal mucosa between them. These ulcers, which varied from 2 cm. to 2 or 3 mm. in diameter, were for the most part irregular in shape, although round

FIGURE 4. *Segments of the Ileum in a Case of Chronic Ulcerative Colitis, Showing Solitary Scattered Ulcers of the Ileum.*

or oval ones were occasionally seen. The long axes of the solitary lesions were either longitudinal or transverse in relation to the ileum. The bases of the ulcers were for the most part fibrotic and granular in appearance. The edges were sharp and well defined. Occasionally, the surrounding mucosa was reddened or congested, but more often the near-by tissues were completely free of evidence of any gross inflammatory reaction. The ulcerations did not have any constant relation to the mesentery as seen in regional enteritis but were distributed over the whole lumen of the small intestine.

None of the 29 specimens showed either diffuse or localized thickening of the wall of the ileum, even though in a few cases the corresponding wall of the colon was excessively thickened, with marked stricture of the intestinal lumen. Although it was quite obvious even to the naked eye that there was

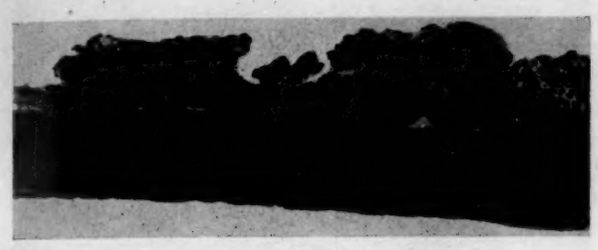

FIGURE 5. *Section of the Entire Wall of the Ileum in a Case of Diffuse Thromboulcerative Colitis.*

Note the mucosal ulcerations. The submucosa, muscularis and serosa are essentially normal. The wall is not thickened (hematoxylin and eosin stain — x 8½).

no great thickening of the involved ileal walls, a measurement of the thickness was made in all cases; it was found that in none was the wall more than 3 or 4 mm. thick. In 26 cases the thickness was within the normal limits of 2 or 3 mm. None of the walls resembled the thick boggy ileal walls seen in specimens representative of regional enteritis. As we expected in the absence of thickening of the ileal walls, none of the 29 ileums revealed any stenosis of the intestinal lumen such as that frequently seen in regional enteritis.

Extent of involvement. The ulcerations may involve only the last few centimeters of the ileum, or they may be scattered over a distance of a few feet. Occasionally, they are found simultaneously in the upper part of the ileum and jejunum. It was possible to determine the exact extent of ileal involvement only in the post-mortem specimens (23 in number) because in only these cases was all of the small bowel available for examination. In the 17 cases in which there was diffuse involvement of the terminal part of the ileum, the average length of ileum affected was 20 cm., the shortest being 4 cm. and the longest 45 cm.

Of the 7 specimens presenting patchy intermittent ulcerations, 3 showed ulcers that extended intermittently over several feet of the lower and upper portions of the ileum, and the other 4 revealed simultaneous involvement of both the ileum and the jejunum with multiple, well defined ulcers. It is of some interest that of the 23 post-mortem specimens, at least 30 cm. of the terminal part of the ileum was involved in 6 and 45 cm. in 3.

In the 6 surgical specimens in which part of the ileum was resected along with the right portion of the colon, only a small segment was available for study, the longest being 50 cm. and the average 20 cm. In only 3 of these surgical specimens was there enough obviously normal ileum proximal to the diseased segment to permit determination of the exact length of the part involved; in these cases 12 cm. of the ileum, on the average, was affected. In the other 3 the inflammatory change was present over the whole segment of the terminal portion of the ileum and ran right up to the point of resection. The length of the ileal segment involved was 4, 5 and 30 cm., respectively, but for reasons stated above, if more of the ileum had been available, perhaps the length of diseased ileum would have been even greater.

Microscopical findings. As was seen from a review of the gross specimens, ulceration and denudation were the predominant features in the mucosal coat (Fig. 5). Ulceration of some degree was present in the ileum of all 29 specimens; in some it was superficial and consisted mostly of erosions and atrophy of the epithelium, but in others it was deep, with a good deal of sloughing and necrosis. An attempt was made to place the ulcers of the ileum, on the basis of microscopical appearance, in the following three groups according to their depth of penetration: ulceration to and including the muscularis mucosae (20 specimens); ulceration through the submucosa (4 specimens); and ulceration through the main muscular layers and serosa with perforation (5 specimens). It was noted that the depth of the ulcers was independent of their gross distribution and character. Many of the solitary ulcers penetrated through all the coats of the bowel, whereas many of the diffuse ulcerations were superficial in character and were associated with little inflammatory invasion of the other coats.

Histologically, in the base of the ulcers the usual three typical zones were seen: zone of necrosis; zone of inflammatory reaction characterized by edema, vascular engorgement and infiltration with polymorphonuclear leukocytes, lymphocytes and plasma cells; and zone characterized by the presence of various amounts of granulation tissue and collagenous connective tissue.

Some authors classify ulcers as acute or chronic. Twenty-four of the specimens showed ulcerations that were chronic, with a predominance of lymphocytes and plasma cells and only a mild degree of

acute polymorphonuclear leukocytic reaction. The 5 specimens that revealed marked degrees of acute inflammatory change were those in which ileal ulcers had resulted in perforation.

In 15 of the 29 cases there was a mild to moderate proliferative thickening of the muscular elements of the muscularis mucosae but not to the marked degree that is seen in cases of regional enteritis. Throughout the submucosa there was a minimal degree of edema, chronic nonspecific granulation tissue and cellular infiltration with aggregations of lymphocytes, mononuclear cells and plasma cells.

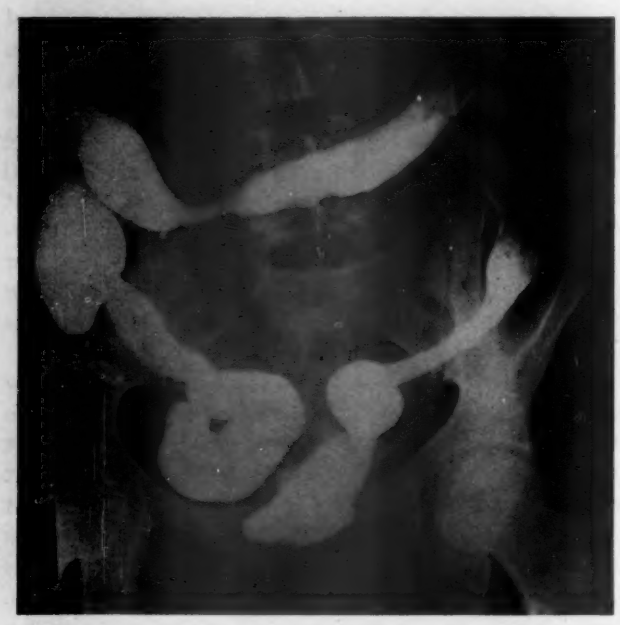

FIGURE 6. *Diffuse Thromboulcerative Colitis of the Entire Colon, with Involvement of More than 30 cm. of the Terminal Part of the Ileum.*

Only the 5 specimens with more acute ulcerations displayed any great degree of polymorphonuclear leukocytic infiltration, and this was found at the base of the ulcers. There was moderate dilatation of the lymphatic channels and congestion of the blood capillaries. Hemorrhage and thrombosis, features described by Bargen[19] as characteristically appearing in the colon, were present in most of the sections but not to the same pronounced degree as seen in the colon. The most characteristic feature was the comparatively minor edematous fibroblastic reaction and fibroplasia, which was minimal when compared with that which is found in the submucosa in cases of regional enteritis.

There was no obvious hypertrophy of the internal and external coats of the muscularis propria in any of the 29 cases. Except in the 5 cases in which there was penetration of the ulcer to the serosal layer and general peritonitis along with the usual degree of thickening with inflammatory exudate, the serosa was normal in all respects in the 29 cases. Small focal collections of epithelioid cells, lymphocytes and giant cells without caseation, referred to as pseudotubercles, were not seen in any of 29 cases of chronic ulcerative colitis, whereas in 30 per cent of the cases of regional enteritis this is a fairly frequent finding. Hadfield,[28] Owens[29] and Shapiro[30] have made reference to this finding in regional enteritis. A study of lymph nodes and mesentery was by necessity omitted from this investigation inasmuch as they were not available for the majority of specimens studied.

Roentgenologic findings. Of the 29 cases, in 10 there were no studies made with the aid of barium enemas, owing to the critical condition of the patient. In 4 of the remaining 19 cases the roentgenologic report mentioned involvement of the terminal part of the ileum by the pathologic process. A recent survey of the roentgenograms revealed definite evidence of ileal disease in another 6 cases, thus making a total of 10 cases of 19 (more than 50 per cent) in which ileal involvement was demonstrated by means of barium-enema studies. The average length of the segment involved as noted in the roentgenologic studies was approximately 1 foot (30 cm.) of the terminal part of the ileum proximal to the ileocecal junction. This involve-

FIGURE 7. *Diffuse Thromboulcerative Colitis of the Entire Colon, with Extension into the Ileum for a Distance of Approximately 60 cm.*

ment was continuous with that of the diseased colon. Eight of the 10 specimens showed at least 30 cm. of involvement, and 2 showed involvement for only a few centimeters according to the roentgenograms. Frequently, the colon in chronic ulcerative colitis is so badly diseased that the roentgenologist does not report the ileal involvement even though roentgenologic evidence is present. Again, the competency or incompetency of the ileocecal valve during the time that barium-enema studies are being made probably plays an important part in determining roentgenologically the point to which the disease has extended into the terminal part of the ileum. Thus, a fair estimate of the true incidence of involvement cannot be obtained on the basis of roentgenologic studies alone (Fig. 6 and 7).

Complications. Clinical symptoms of mechanical obstruction of the small bowel due to stenosis of the lumen were not observed in any of the 29 cases of chronic ulcerative colitis in which the ileum was involved by ulcerative disease. This was to be expected on the basis of the study of the gross specimens, inasmuch as not a single specimen presented stenosis of the lumen of the small bowel or excessive thickening of the wall, which was found routinely in the cases of chronic regional enteritis.

It was impossible to estimate how often the ulcerations of the involved ileum gave rise to severe hemorrhage or loss of fluid because the process in the colon alone was enough to account for these occurrences. However, excessive loss of fluid from the ileum following an ileostomy has been shown by Crandon, Kinney and Walker[16] to arise from these ulcerations. None of the 8 patients in this series who underwent ileostomy continued to bleed from the ileal stoma or to lose an excessive amount of fluid after operation, but it must be remembered that all these patients succumbed very shortly after operation. Only 1 of the 8 patients survived longer than three weeks, and he died within two months of the date of ileostomy.

Perforation of the ileal ulcers is without doubt the most dangerous of all the complications of ileal involvement in chronic ulcerative colitis because it apparently invariably results in generalized peritonitis and death. As mentioned above, in 5 of the 29 cases (17 per cent) this complication occurred. One patient presented six solitary ulcers, one of which had perforated after ileostomy. This patient died three weeks later of generalized peritonitis, and multiple ulcers were demonstrated in the ileum proximal to the ileal stoma. Crandon, Kinney and Walker[16] reported a 24 per cent incidence of perforative lesions of the small bowel in cases of ulcerative ileitis.

Clinical significance. In attempting to evaluate the clinical significance of involvement of the ileum in chronic ulcerative colitis it should be demonstrated whether this involvement occurs relatively early in the course of the disease or whether it is, for the most part, a very late complication — a sort of terminal event in the downhill progress of the disease. Therefore, it is important to know when the ulcers make their appearance in the ileum. Crandon, Kinney and Walker[16] have shown that ileal involvement may appear early in the course of the disease. In an analysis of our 29 cases the only way that we could determine whether the ileum was involved relatively early or whether the involvement occurred merely as a terminal event in the course of the disease was by means of a study of the cases in which there was roentgenologic evidence of ileal involvement or by means of a study of the surgical cases. In 3 cases disease of the ileum was demonstrated roentgenologically one month, two months and three years respectively before death. In the 6 surgical cases, from one to seven years elapsed from the time that involvement was described at operation to the time of the present study. Certainly, in none of these cases could the involvement be called a terminal event of an intractable colitis; therefore, its occurrence must have been of more than academic interest.

A further analysis was made to determine whether the severity or course of colonic disease had any relation to the involvement of the ileum. We were interested in seeing whether the patients who had acute fulminating ulcerative colitis that might terminate fatally in a very short time were more prone to have ileal involvement than those with disease that was characterized by a long, chronic course of remissions and exacerbations. In 8 of the 23 cases in which autopsy was performed there had been a rather acute fulminating course of a year or less from the onset of symptoms to death; in the other 15 cases the course was chronic. Therefore, it is apparent that ileal involvement occurs both in cases of acute fulminating disease and in those of long-standing chronic disease. It is also of clinical significance that in only 1 of the 8 cases of acute disease were the ulcerations so severe that they resulted in perforation of the ileum. In the other 4 cases of perforation the disease was definitely chronic.

What, then, is the importance of ileal involvement in chronic ulcerative colitis? How may the prognosis be affected by this involvement? When an operation such as ileostomy is performed in this disease and the terminal part of the ileum is simultaneously involved in the inflammatory process, a high mortality and a poor operative result may be obtained.

Ileostomy in chronic ulcerative colitis is accompanied by a very high mortality. In 1932 Bargen, Brown and Rankin[31] reported a mortality of 66 per cent for emergency and 50 per cent for elective ileostomy. In 1935 McKittrick and Miller[12] observed a mortality of 35 per cent. Cave and Thompson,[32] in 1941, reported an over-all mortality

of 25 per cent for ileostomy, the rate being 50 per cent for emergency operations and 9 per cent for elective operations. In the same year Lahey[33] reported a mortality of 20 per cent for ileostomy in chronic ulcerative colitis. Many circumstances have been held responsible for the high mortality rate and the high incidence of failure of ileostomy in this disease. We wish to emphasize the fact that involvement of the ileum by ulcerative disease is one of the commonest and yet infrequently mentioned factors in the high mortality rate and the frequent failure of ileostomy in chronic ulcerative colitis.

Of course, it is agreed by most surgeons that extensive exploration of the peritoneal cavity and excessive handling of the diseased bowel in the acute stage of chronic ulcerative colitis is contraindicated. Nevertheless, enough exploration and examination of the distal part of the ileum must be done to exclude the diagnosis of inflammatory changes in this segment. Dennis[17] has emphasized this point. He routinely sections a small segment of ileum for gross examination of the mucosa prior to establishing the site for the ileal stoma to avoid placing the stoma in a diseased segment of the small bowel. Involvement of the ileum in chronic ulcerative colitis is probably a definite contraindication to the performance of ileostomy unless the ileal stoma can be placed well above any area in which there is gross or microscopical involvement. Eight of the 23 patients who came to autopsy had had a previous ileostomy. The longest period of survival was sixty days, and the shortest five days.

Summary and Conclusions

A study is presented of 23 necropsy specimens of the bowel in cases of chronic ulcerative colitis of the diffuse thromboulcerative variety with ileal involvement encountered at the Mayo Clinic from 1935 to 1946. In addition, the ileum in 6 surgically removed specimens of the bowel in cases of chronic ulcerative colitis with ileal involvement was studied. These 29 specimens were selected from 81 autopsy and 22 surgical specimens of the bowel in cases of chronic ulcerative colitis in which the proctoscopic and roentgenologic criteria outlined were met. The incidence of ileal involvement in the 103 cases was 28 per cent. Six of the 22 surgically removed specimens showed ileal involvement, giving an incidence of 27 per cent; 23 of 81 autopsy specimens revealed such involvement, giving an incidence of 28 per cent. The incidence of ileal involvement reported in the literature varied from 1.3 to 39 per cent.

The average length of the segment of ileum affected in the cases in which the pathologic changes were diffuse was 20 cm., with variations from 4 to 45 cm. In 7 of the 29 cases solitary ulcers were present, sometimes extending throughout the length of the small bowel.

The nature of the disease in the ileum was similar to that found in the colon. It was essentially denuding and ulcerative. Twenty-two cases were diffusely ulcerative, and in 7 the ileum presented multiple solitary ulcers.

Roentgenologic evidence of ileal involvement was found in 10 of 19 cases in which barium-enema studies were carried out.

Perforation of the ulcerations of the ileum, with generalized peritonitis, was a very serious complication that occurred in 5 of the 29 cases, or 17 per cent. In 4 of the 5 cases perforation occurred almost immediately after the performance of ileostomy.

The duration of the disease showed no definite relation to the incidence of ileal involvement. Eight of the 23 patients who came to autopsy (35 per cent) ran an acute fulminating course of one year's duration or less, whereas the remaining 15 patients (65 per cent) had a long chronic course lasting from five to fifteen years.

Ileal involvement in chronic ulcerative colitis is not necessarily a terminal event of an intractable colitis as is assumed by many authors. In 9 of the 29 cases (31 per cent), the ileum was definitely shown, on the basis of surgical or roentgenologic data, to be involved relatively early in the course of the disease.

The ileum is involved in chronic ulcerative colitis more often than is generally realized, and this finding should therefore be looked for in all cases of diffuse chronic ulcerative colitis.

Knowledge of the presence and extent of ileal involvement in chronic ulcerative colitis is an important consideration if surgical treatment is deemed necessary.

Ileostomy for chronic ulcerative colitis performed through a segment of ileum that is the site of ulcerative inflammatory changes will probably produce a poor operative result. Perhaps this is one of the important considerations responsible for the high mortality associated with ileostomy in the treatment of this disease.

Involvement of the ileum is probably one of the factors that retard the healing process in the colon in chronic ulcerative colitis.

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CANCER OF THE LOWER LARGE BOWEL*

Results in 100 Cases

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THE intent of this survey is to present an investigation of facts pertinent to the care of 100 consecutive patients with cancer involving the lower segments of the large bowel and to offer an appraisal of the therapeutic effort employed in their management.

This series includes both service and private patients at the Maine General Hospital, private patients at the Eye and Ear Infirmary and the Mercy Hospital, all of Portland, and one or more patients treated in each of six other institutions in outlying towns. It is obvious, then, that no one of these patients received all the advantages available in the university or large medical center. Furthermore, some of the results obtained reflect earlier and less experienced endeavor before the advent of the sulfonamide or antibiotic remedies and before the value of fluid, electrolytic, vitamin and protein deficiencies was fully appreciated.

From the current literature and from my own observation, the impression is gained that cancer of the large bowel is neither diagnosed nor subjected to operation appreciably earlier than it was ten or more years ago. Yet intestinal cancer, like any malignant lesion, has an early stage when the growth is small, sharply circumscribed and therefore readily extirpated. Just how long cancer in its early phase exists in the bowel without producing symptoms is yet to be determined; unfortunately, the process remains quiescent without manifestation until certain complications signal the presence of danger.

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It is common knowledge that when a tumor of the bowel becomes sufficiently ulcerated the process may manifest itself by either gross or occult blood in the stool — an occult blood loss at times so insidious that only anemia is evident, the malignant lesion being otherwise asymptomatic. A cancerous mass, having acquired sufficient size and inflammatory reaction, or having compromised the bowel lumen, may produce enough irritation to promote frequent or liquid stools and in some cases dejections composed largely of mucus, either with or without local or abdominal discomfort as an associated symptom. These manifestations are the obvious signs and symptoms that warn both patient and physician of impending danger, but too many practitioners appear to be unmindful of the fact that such complaints indicate not early cancer but the complications of a well established malignant tumor urgently in need of attention.

Inasmuch as complaints referable to the terminal segments of the large intestine ordinarily bespeak the existence of a benign disorder, the average person with such an ailment is apt to assume that he is suffering from one of the more prevalent conditions such as piles, colitis and diarrhea and often employs self-medication for months. That the physician too often acquiesces in this frequently fallacious assumption or initiates the idea himself, instead of insisting that the patient have the benefit of a thorough rectal examination, is perhaps only natural since it has been estimated that the average practitioner rarely encounters yearly more than one or two patients with cancer of the rectum and, therefore, is not rendered sufficiently cancer-

conscious to recognize the fact that a malignant tumor should be the primary consideration to be confirmed or rejected only after appropriate investigation. Physicians do not appear constantly alert to the fact that 70 per cent of all cancer of the large intestine can be either actually palpated or made accessible to the eye by use of the sigmoidoscope, whereas it frequently escapes detection by the conventional barium-enema x-ray study.

Although progress in the field of establishing the presence of cancer in the earlier phases of its development is grievously lacking, ground has unquestionably been gained in the field of therapy. In recent years a greater number of the more extensive and inaccessible malignant tumors of the alimentary tract have been resected with increasing degrees of success. The fact has become well established that morbidity and mortality rates in the management of colonic and rectal cancers have definitely lowered, and, since the healing process of the body is influenced by a variety of factors, few surgeons have been sufficiently speculative to ascribe this more recent decline to any solitary factor.

In 1942, however, in reporting his experience with one-stage abdominoperineal resections, Jones[1] noted that the incidence of abdominal-wound infection was in direct relation to the number of peritoneal and pulmonary complications. He expressed the opinion that postoperative peritonitis was always secondary to an infected wound, and he implied that, by removal of the hazard of infection from the incision by the use of steel wire sutures, peritoneal infection had been practically eliminated. Furthermore, during this period of the metallic suture, which was the only change in management, the incidence of hospital deaths dropped from 12 to 4.5 per cent, and he stated: "I am convinced that this type of closure is accountable for most of the success." During the year 1940 the morbidity and mortality in colonic and rectal surgery at the Mayo Clinic, according to Pemberton,[2] also dropped rather abruptly from approximately 15 to 5 per cent. This improvement was credited not to a change in technic or management but to the activity of the sulfonamide compound. Furthermore, because of that same agent, the two most lethal complications of large-bowel resection fell precipitously, peritonitis from 6.1 per cent before the sulfonamide era to 1.8 per cent after it and, correspondingly, bronchopneumonia from 2.2 to 0.7 per cent.

Although the years 1940 and 1942, as mentioned respectively by Pemberton[2] and Jones,[1] may have witnessed a substantial decline in morbidity and mortality owing to the influence of single, solitary factors such as the innocuousness of suture material on the one hand and the bactericidal effect of sulfonamides on the other, it is noteworthy that the year 1942 has been designated by McKittrick[3] as the period of transition from the earlier to present methods. He has expressed the opinion that as the result of adherence to meticulous technic and essential basic surgical principles, without dependence on chemotherapeutic and antibiotic agents or on staged operations, the death rate of 11 per cent prior to 1942 has fallen to 3.6 per cent. In the present survey it is an interesting coincidence that of the first 50 patients, the 40 who underwent resection prior to the year 1941 suffered a 20 per cent hospital mortality but that of the second 50 patients the 45 who were subjected to similar treatment experienced no mortality.

An appraisal by the surgeon of his own work should be of assistance in modifying methods or practices for the benefit of those patients entrusted to his care. A prerequisite, of course, is that he know what is being accomplished by other workers in the same field of endeavor under similar as well as more favorable conditions and that he be familiar with the natural history of the disease under consideration. The latter information on rectal cancer in this country was made available in 1935 when Daland, Welch and Nathanson[4] reported the end results in 100 untreated cancers of the rectum. In their record we find that, although a single patient lingered for forty-nine months, the median length of life was only fourteen months from onset of symptoms to death. All patients were miserable while they awaited the inevitable, and all died with cancer. Also during that period from 19 different hospitals, 10 of which were in Boston, these investigators found the prevailing operative mortality

TABLE 1. *Operative Procedures in 100 Cases of Rectal and Rectosigmoidal Cancer, 1933–1946.*

No. of Cases	Procedure	Deaths	
14	Colostomy	6	
1	Fulguration	0	
9	Loop colostomy, with posterior resection	0	
5	Anterior resection and colostomy	2	
22	Lahey, two-stage resection	5	
14	Anterior resection, with end-to-end anastomosis	0	
2	Cecostomy, with abdominoperineal resection	0	
33	Abdominoperineal one-stage resection	1	
85	Resection	8	(9.4 per cent)

TABLE 2. *Hospital Deaths.*

Group	Fatal Complications	No. of Deaths
First 50 patients (40 resections)	Bronchopneumonia	2
	Peritonitis	1
	Volvulus, small bowel	1
	Cerebral hemorrhage	1
	Undetermined (no autopsy)	3
Second 50 patients (45 resections)	0	0

to be 26 per cent and, operative deaths excluded, the five-year survival rate to be 41 per cent. Since these findings were recorded, mortality and longevity figures have continuously improved.

The various types of operative procedure employed in the group of patients here presented are recorded in Table 1. The wisdom exercised in performing 14 segmental resections with end-to-end anastomosis for cancer of the rectosigmoidal region can be properly questioned since such an operation does not remove the greatest possible amount of contiguous and regional lymph-node tissues. But regardless of the fact that Glover and Waugh[5] justify the less radical operation with preservation of the anal sphincter as a result of their investigation of lymph-node metastasis in cancer of the "recto-sigmoid region," and despite the fact that Gilchrist and David[6] present evidence against the advisability of such a procedure as a result of an investigation of the same problem, under certain conditions it has seemed to me that the interests of the patient could be best served by the less radical operation. Complete loss of vision, loss of vision with profound deafness, liver metastasis and an error in interpreting by palpation two hepatomas as metastatic growths were factors that influenced

TABLE 3. *Contact Tissues or Organs Resected en Bloc with Primary Cancer.*

STRUCTURE	NO. OF CASES	SURVIVAL
Uterus, adnexa	1	2 da.
Uterus	1	4 yr.
Posterior vaginal wall and labium	2	3 yr.*; 4 yr.*
Posterior vaginal wall	2	0†; 2 mo.
Bladder, peritoneum and adventitia	1	11 yr.
Ileum	1	9 yr.
Appendix	1	3 yr.

*Patient living.

†Patient died on operating table.

me to preserve the anal sphincter. A better service to others in this sub-group might have been derived from the more radical Miles resection.

Hospital deaths for all patients who underwent resection are listed in Table 2.

The one feature of surgical treatment of large-bowel cancer on which all surgeons of experience appear to be in accord is that a procedure aimed at relief that fails to remove the primary growth, except possibly in the presence of a high degree of obstruction, gives little or no alleviation. Consequently, operative procedures have become more extensive to accomplish this end. As indicated in Table 3, it has likewise been my practice to remove tissues or organs invaded by contact spread, even in the presence of liver metastasis or advanced age of the patient, the eldest being aged eighty-three years.

A critical check of the complications in any series of major procedures is often sobering, if not instructive. Such a review may yield information that will prevent the repetition of undesirable occurrences and permit the earlier recognition and treatment of others, thereby reducing morbidity and mortality. Inasmuch as it was my custom to manage the impaired bladder function incident to operative trauma by use of the inlay catheter for seven to twelve days after operation, all patients included in this survey must have had some degree of urinary-tract infection, and yet there were apparently no severe or protracted symptoms of cystitis. With two exceptions the patients were able to void with little or no difficulty at the time of dismissal from the hospital. These two irregularities and all other serious, nonfatal complications are recorded in Table 4.

The circumstance that new cancers develop and others reappear years after the initial lesion has been removed presents another aspect of the present-day attitude toward management. The

TABLE 4. *Serious Nonfatal Complications in 85 Resections in 100 Cases.*

COMPLICATION	NO. OF CASES
Urinary obstruction	2
Sloughing membrane of urethra	1
Encephalopathy	1
Retraction of colostomy stoma	1
Small-bowel obstruction	4
Thrombophlebitis and embolism	2
Separation of suture line	2

success of a second resection, as recorded by Dunphy,[7] Young[8] and others, serves to stress the importance of a thorough examination of the patient whenever disorders suggesting cancer reappear, since long periods of arrest may follow a radical reoperation, with gratifying results to both patient and physician.

Although it has been impossible to determine in my own group of patients how many actually became victims of a recurrence or of a new cancer, both conditions were known to have occurred. One patient has remained in good health for a period of seven years after the removal of the rectal stump with its recurrent cancer, which was discovered and resected twelve months after an anterior resection and colostomy in another hospital. A second patient lived more than six years after the removal of a new sigmoidal cancer, which appeared approximately four years after the extirpation of a malignant lesion of the rectum. A Miles resection, performed on a third patient, disclosed a rectosigmoidal cancer that neither at the operating table nor on examination by a pathologist revealed lymph-node invasion. Unilateral metastatic cancer became manifest six years and three months later in the inguinal and iliac lymph nodes. The perineal and abdominal-wall tissues were free from any recurrence; urinary-tract signs and symptoms were in

abeyance, and a roentgenogram of the spine revealed nothing abnormal. On opening the abdomen I found no disease of the presacral region, peritoneum, liver or organs or tissues other than those mentioned. Consequently, the inguinal and iliac lymph nodes were resected according to the method of Taylor and Nathanson.[9] The nodes were firm and not adherent to important structures. The largest node measured 3.2 cm. in diameter. Two years and three months later, re-examination revealed that the patient was doing manual labor at the age of seventy-three years. There had been no evidence of a local recurrence or involvement of the opposite groin, but for a month he had been annoyed by a "burning sensation" on voiding and a urinary frequency of two or three times nightly. Microscopical examination of tissue obtained by a transurethral resection revealed prostatic cancer. His response to prostatic revision has been satisfactory, and he continues to work.

TABLE 5. *Survivals* among 100 Cases of Rectal and Rectosigmoidal Cancer.*

DATUM	NO. OF CASES
Radical resections	85
Patients surviving resection	77
Patients lost to follow up	0
Death in less than 5 yr.	36
Death after 5 or more yr.	5
Patients living less than 5 yr.	16
Patients living 5 to 10 yr.	16
Patients living 10 or more yr.	4

*Five-year survival rate to June 9, 1948, excluding hospital deaths was 32.46 per cent (25 cases).

The survival periods for the entire group to June, 1948, are summarized in Table 5.

SUMMARY

Observations on a group of 100 consecutive patients with cancer involving the rectum and rectosigmoid region are presented. The pressing need for earlier recognition of this type of cancer is again emphasized. Results obtained in terms of hospital deaths and survival rates are recorded, and fatal and significant, nonfatal complications are enumerated. Success obtained from a second resection in a very limited number of patients with recurrent or new cancer is noted. Although insufficient time has elapsed since treatment of the last patient to permit determination of the final figures on five-year survivals, attention is called to the fact that the trend of the immediate postoperative hospital death rate is definitely downward.

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REPEATED NEPHROTIC EPISODES WITH NORMAL URINE, SERUM PROTEIN AND CHOLESTEROL IN THE EDEMA-FREE INTERVALS*

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A PATIENT in whom the nephrotic syndrome appeared and disappeared on three occasions has been observed from 1933 to 1948. During each remission albuminuria and edema disappeared, and the serum protein and cholesterol values returned to normal. Only 3 similar cases have been located in the extensive literature on the subject. The details of this case including the many observations made over the period of fifteen years and a review of the relevant literature are the subject of this report.

CASE REPORT

M. C. (B.I.H. No. 18029), a 17-year-old boy, entered the hospital on April 17, 1933, because of swelling of the lower eyelids and over the sacrum. Until December, 1932, he had been well except for chronic eczema of the right hand. At that time swelling of the legs developed; later, swelling of the thighs and lower eyelids and over the sacrum was noted. Except for the edema, which had continued until admission to the hospital, there had been no symptoms or history of a respiratory-tract or other infection or smoky or bloody urine.

Physical examination revealed a tall, pale, poorly nourished boy with definite puffiness of the eyelids and pitting edema over the sacrum but no edema elsewhere. The fundi were normal as were the throat, heart, lungs and abdomen. The blood pressure was 104/75. Examination of the urine showed a specific gravity of 1.035 and a large amount of albumin, but the sediment was normal. During the hospital stay of 1 week, the urine specific gravity ranged from 1.018 to 1.035. Additional specimens showed doubly refractile bodies and an occasional white cell and cast. Phenolsulfonephthalein excretion was 55 per cent in 2 hours and 10 minutes after the intramuscular injection of 1 cc. of the dye. Examination of the blood revealed a normal nonprotein nitrogen, low serum protein and serum albumin and elevated serum cholesterol values (Table 1). During a 1-week stay in the hospital the albuminuria diminished to a minimal amount, and the edema entirely disappeared. After discharge on April 25 albuminuria decreased further, finally disappearing in June.

Routine physical examination on admission to the first-year class at Harvard College in September disclosed no edema. The urine had a specific gravity of 1.020 and was free of albumin, and the sediment was normal. The blood pressure was 110/70. In June, 1934, the findings were the same. At that time, blood chemical studies were normal (Table 1).

On October 17 the patient was admitted to the Stillman Infirmary of Harvard University because of malaise and anorexia, which had developed without antecedent infection.‡ Edema of the extremities had recurred. The urine showed considerable albumin, the specific gravity ranged from 1.014 to 1.028, and the sediment contained occasional red and white cells, casts and many cells with "fat globules." Blood chemical studies were similar to those in the first episode (Table 1). Toward the end of the first week of the infirmary stay the edema disappeared. Upon discharge on November 27, the patient was free of edema but showed massive albuminuria, hypoproteinemia and hypercholesterolemia. During December marked edema of the eyelids, legs and sacrum recurred. Examination of the urine revealed massive albuminuria and a specific gravity of 1.024, and the sediment contained occasional red cells and casts.

He was readmitted to Stillman Infirmary from January 24 to February 1, 1935, with mild impetigo. The edema disappeared as the impetigo cleared. The albuminuria gradually diminished and finally disappeared in April.

Many examinations from May, 1935, to March, 1945, showed no edema. During this 10-year period the urine was normal except in February, 1936, when after a cold and sore throat a minimal amount of albumin and 2 or 3 red and white cells per high-power field in the sediment were noted. In May, 1937, postural albuminuria was found. In April, 1938, the patient suffered with streptococcal sore throat and in July because of acute suppurative appendicitis he underwent an appendectomy; neither of these infections was accompanied by albuminuria except for a minimal amount on the day after operation.

The serum proteins and cholesterol were normal throughout this remission (Table 1). In September, 1940, when he enlisted in the Army, and in April, 1943, when he entered officers' candidate school, urine examinations were negative.

On March 1 and 2, 1945, while overseas, he suffered with a boil on the wrist for which he was given 120,000 units of penicillin with prompt relief. Three weeks later generalized anasarca recurred. This gradually diminished with frequent intramuscular injections of mercupurin and intravenous infusions of blood plasma. On May 23 he still showed slight edema of the legs and was returned to this country. The edema of the legs persisted, and puffiness of the face and lower eyelids recurred each morning until August, when he was discharged from the Army with the diagnosis of "nephritis, chronic, glomerular, nephrotic stage, moderate, cause undetermined."

Frequent examinations of the urine during the early phase of this nephrotic episode showed massive albuminuria and erythrocytes. Massive albuminuria persisted, and the specific gravity ranged between 1.023 and 1.028. Blood chemical studies revealed hypoproteinemia, hypoalbuminemia, hypercholesterolemia and normal nonprotein nitrogen (Table 1). The blood pressure fluctuated around 120/80.

From August, 1945, to June, 1948, the patient was free of edema. On August 7, 1945, examination of a single specimen revealed no albumin and a normal sediment; the specific gravity was 1.030. In January, 1946, seven consecutively voided urines collected according to a method described elsewhere[1] showed no albumin, cells or casts; the specific gravity ranged between 1.027 and 1.040. Chemical quantitation§ of albumin in these specimens of urine showed 3 to 7 mg. per 100 cc., which is normal. At that time blood chemical studies revealed normal nonprotein nitrogen, total serum protein and serum albumin; the cholesterol was 356 mg. per 100 cc. (Table 1). Physical examination was negative except for dry scaling lesions on the wrists. The blood pressure was 110/70. From June 10 to June 15, 1946, he was hospitalized because of a carbuncle of the finger, with lymphangitis of the forearm and axillary adenitis. Incision and drainage of the carbuncle and frequent intramuscular injections of large amounts of penicillin brought about prompt recovery. Examination of eleven consecutively voided specimens of urine showed no albumin, normal sediments and specific gravity between 1.006 and 1.032. Blood chemical studies were normal (Table 1). The blood pressure was 130/80. The scaling of the wrists was diagnosed as "atopic dermatitis" by a skin consultant. In September, 1947, during a follow-up visit, physical examination was negative except for a few scaling lesions on both wrists. The blood pressure was 118/70. Seven consecutively voided urine specimens[1] showed no albu-

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min, with normal sediments, the specific gravity ranging between 1.023 and 1.028. In January, 1948, the patient was given frequent intramuscular injections of large doses of penicillin for a carbuncle on the neck, with prompt recovery. Urine examinations were not performed. Edema did not recur. In June during a follow-up visit, physical examination was negative except for very few scaling lesions on one wrist. The blood pressure was 120/80. Eight consecutively voided urines[1] showed no albumin; the sediments were normal, and the specific gravity ranged between 1.018 and 1.029. Blood chemical studies were negative.

TABLE 1. *Summary of Laboratory Findings.*

DATE	URINE					
	NUMBER OF SPECIMENS EXAMINED*	SPECIFIC GRAVITY	ALBUMIN	FORMED ELEMENTS AFTER CENTRIFUGATION (PER HIGH-POWER FIELD)		
				Red Blood Cells	*White Blood Cells*	*Casts*
First nephrotic episode:						
4-17-1933 to 4-20-1933	3	1.020 to 1.035	+++ to ++++	0	0-3	0-1
4-25-1933	1	1.018	+	0	1-2	0
First remission:						
9-1933 to 6-1934	2	1.020	0	0	0	0
Second nephrotic episode:						
10-17-1934 to 2-20-1935	7	1.014 to 1.028	+++ to ++++	Occasional	0-8	Occasional
3-20-1935	1	1.024	++	Occasional	Occasional	0
Second remission:						
5-9-1935 to 9-11-1935	6	1.020 to 1.028	0	0	0	0
2-10-1936	1	1.025	+	2-3	2-3	0
2-12-1936 to 9-9-1936	7	1.024 to 1.030	0	0	0	0
5-19-1937	1	1.025	0	0	0	0
	2	1.015 to 1.025	+†	0	0	0
6-19-1937 to 7-22-1938	10	1.020 to 1.026	0	—	—	—
7-23-1938	1	1.022	+	0	0	0
7-26-1938 to 4-1943	11	1.018 to 1.030	0	0	0	0
Third nephrotic episode‡:						
3-23-1945 to 5-15-1945	Very frequent		++++	Positive	0	0
5-23-1945 to 8-2-1945	Many		++++	0		
	5	1.023 to 1.028	++++	0	0	0
Third remission:						
8-7-1945	1	1.030	0	0	0	0
1-30-1946 to 1-31-1946	7	1.027 to 1.040	0 §	0	0	0
6-10-1946 to 6-15-1946	11	1.006 to 1.032	0	0	0	0
9-11-1947	7	1.023 to 1.028	0	0	0	0
6-12-1948	8	1.018 to 1.029	0	0	0	0

*Examinations for sugar negative.
†Postural albuminuria.
‡Complete data not available from Army hospitals.
§Quantitative albumin, 3-7 mg. per 100 cc.

DISCUSSION

The nephrotic syndrome is characterized by massive albuminuria, hypoproteinemia, hypercholesterolemia and edema. It occurs most often in glomerulonephritis. Other causes are lipoid nephrosis, intercapillary glomerulosclerosis, renal amyloidosis, syphilis, gold intoxication, renal-vein thrombosis,[2, 3] lupus erythematosus[4] and mercury poisoning.[5, 6]

The course of the nephrotic syndrome in these conditions shows considerable variation. In some, edema and albuminuria disappear, and the blood proteins and cholesterol return to normal levels. In others, although albuminuria persists, the edema continues with very little change, or it may decrease or even disappear for a time only to recur; it may also diminish gradually and disappear coincident with a decrease in albuminuria, development of impairment in renal function, hypertension and, later, renal insufficiency.

However, cases of repetitive nephrotic episodes with normal urine, total serum protein and cholesterol in the edema-free intervals have rarely been

observed. Leiter,[7] Fishberg[8] and Wilson,[9] in their wide experience with renal disease, have never observed a case of this type. In an excellent review of the literature Bradley and Tyson[10, 11] did not describe such cases. Recently, a sixteen-year-old girl with petit-mal seizures was described[12] in whom the nephrotic syndrome appeared during the rotic symptoms and signs to the time of writing.[13]

Addis[14] recently described 2 cases in which the nephrotic syndrome appeared and disappeared on two occasions as follows:

Case B. H., female, aged 25 — Edema and proteinuria found October 1923. Both went away in the autumn of 1924, but proteinuria and later edema reappeared in 1925

TABLE 1 (*Continued*).

Blood						Blood Pressure
BLOOD NONPROTEIN NITROGEN	TOTAL SERUM PROTEIN	SERUM ALBUMIN	SERUM GLOBULIN	SERUM CHOLESTEROL	HEMOGLOBIN	
mg. per 100 cc.	*gm. per 100 cc.*	*gm. per 100 cc.*	*gm. per 100 cc.*	*mg. per 100 cc.*	%	
24–32	4.5	1.5	3.0	440–480	80	100/70
	4.3	1.5	2.8			
26	4.4	1.8	2.6			108/80
	6.4	4.8	1.6	184	—	110/70
	4.5	2.0	2.5	580	75	118/70
	5.5					
26–31	5.4	3.3	2.1	114–178	—	98/60 to 110/70
	5.7	4.0	1.7			
30	6.82			145–187	90	100/60 to 110/60
31–37	7.3	4.3	3.0	173–230		
	6.1					
—	—	—	—	—	94	90/50 to 128/72
					87	
27–31	7.1	4.6	2.5	166–250	80	110/70
	6.7				85	
Normal						
Normal	5.04	2.16	2.88	588		120/80
23	8.4	5.2	3.2	356		110/70
29	7.14	5.01	2.13	167	100	130/80
—					100	118/70
—	8.5	5.0	3.5	185	—	120/80

administration of tridione and disappeared upon withdrawal of the medication on three different occasions. Hypertension and microscopical evidence of hematuria were found during the second nephrotic episode, and elevation of the blood urea nitrogen to 47 mg. per 100 cc. was found in the third nephrotic episode. This report was published five months after recovery from the third nephrotic episode, and the patient had remained free of neph-

and continued until October 1925. No recurrence of either edema or proteinuria up to 1938.

Case P. L., male, aged 7 — Edema and proteinuria lasted for less than a month in 1935, and both disappeared. Both returned in 1938. The edema quickly went, but the proteinuria did not disappear until 1940.

In my case reported above the first two nephrotic episodes, in 1933 and 1934-1935, developed without definite antecedent cause. It is possible, however, that the first two nephrotic episodes were related

to secondary infection of the eczematous lesions. The third episode in 1945 followed a boil on the wrist, but the patient had had other infections including a streptococcal sore throat and acute suppurative appendicitis in 1938, a carbuncle on a finger in 1946 and a carbuncle on the neck in 1948 without recurrence of the nephrotic syndrome. Although the evidence does not permit one confidently to relate infection to the recurrent nephrotic episodes this possibility should be explored in patients who exhibit this phenomenon.

In the case reported by Barnett et al.[12] the findings of hypertension and microscopical hematuria in the second nephrotic episode and elevation of the blood urea nitrogen in the third nephrotic episode suggest that those episodes were due to acute glomerulonephritis of short duration and precipitated by tridione. In my case reported above there was never hypertension or nitrogen retention. The finding of minimal hematuria in the second and third nephrotic episodes may mean that these episodes were due to acute glomerulonephritis. However, in nephrosis "an occasional red blood cell in a high power field of centrifuged specimen"[15] may be seen. Addis[14] found by his special technic that in his patients the rate of red-cell excretion was within normal limits and that in the few cases in which abnormal numbers were found succeeding counts showed few red cells or none.

Leiter[7] recently pointed out that "it would be easy to overlook a slight albuminuria continuing between nephrotic episodes if one did not examine concentrated urine specimens carefully." In my case presented above, repeated examinations of concentrated specimens of urine during the intervals between the nephrotic episodes and after the last episode revealed no albumin except during the second remission (Table 1). During this ten-year period, thirty-nine urine examinations were performed; thirty-five showed no albumin, whereas four showed minimal amounts of albumin under the following conditions: after a cold and sore throat, during a test for postural albuminuria, and on the day after operation for acute suppurative appendicitis. In the cases described by Addis[14] "the urinary evidence of a renal lesion disappeared only to recur at a later date."

The absence of continuous albuminuria between nephrotic episodes in my case reported above and in those of Addis[14] and Barnett et al.[12, 13] is not consistent with chronic glomerulonephritis. In the latter condition, although edema may fluctuate from time to time, the albuminuria is constant and continuous. The nature of the renal lesion "that comes and goes"[16] in the case reported above and in the cases of Addis[14] is unknown.

The details of this remarkable case were discussed with Dr. Henry A. Christian, who states that it is unique in his extensive experience and who has presented certain aspects of the case in his recent monograph on renal disease.[17]

Summary

The pertinent data in a patient in whom the nephrotic syndrome appeared and disappeared spontaneously on three occasions are presented. During each remission, albuminuria and edema disappeared, and the serum proteins and cholesterol returned to normal values.

The relevant literature is discussed.

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MEDICAL MILITARY SCIENCE

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BOSTON

DURING the past two years, a new course has appeared on the curriculum of forty-nine American medical schools. "Medical Military Science" or "Military Medicine" is its title. The Army provides its instructors, and the medical school is its sponsor. The students taking this course will shortly be members of the medical profession. That profession deserves to be informed of the training the neophyte has received in this post-war version of the Medical Reserve Officer Training Corps (ROTC).

As in the past, military medicine is an elective course offered to the student body. It is a progressive course, through the four years of medical school, meeting one hour weekly. Students are of two categories: those who are pursuing it simply as an elective course, and those who are enrolled in the Reserve Officers Training Corps. The latter must meet rigid physical standards and sign a contract at the beginning of their third year to complete the course and to attend a summer camp for training for six to eight weeks during the summer recess, after completion of the second or third year. In return, they are paid a small stipend by the Government and, on satisfactory completion of the course, are offered a commission as a first lieutenant in the Medical Corps Reserve.

The course is designed to supplement the medical-school curriculum, which prepares the student for the practice of civilian medicine. The medical school teaches him the technics involved in providing ideal medical care for the individual patient, and indoctrinates him with the fundamentals of public-health organization and practices. Military medicine introduces the student to a broader concept of mass medicine, to the problems of the situation where the facilities of standard medical practice are overburdened — in short, to the approach that must be used to cope with a catastrophe. Although it is within the realm of possibility that war will be outlawed, catastrophes will always constitute a problem in the planning of medical care. To make the material generally pertinent, the presentation is usually based on the line of action to be followed in case of catastrophe or disaster — fire, flood, blast or war.

Intelligent medical service in a catastrophe can be rendered only by planned action, with consideration of personnel densities and exposure to hazards. Medical facilities will be weighted in favor of the larger city; preparations will be made for casualties where explosive materials are stored in a burning warehouse. Conversely, the potentialities of the situation must be known, lest the rescuers themselves become casualties. Efficient disaster relief is not spontaneous, but is dependent on prior planning and organization. The best standard for a study of these considerations is found in the Army, since its medical department is designed to cope with the catastrophes produced by enemy action.

In the first year of the course in military medicine, the organization of the Army is studied from the point of view of its effect on the disposition, number and severity of the sick and wounded. Tactics are briefly considered from the point of view of their influence, adverse or beneficial, on the problem of providing medical care. With the medical problem thus established, the over-all medical organization is taken up, demonstrating the deployment of equipment, skills and personnel to cope with the actual and potential situation, together with the integrating mechanisms (chain of command) that maintain unity of objective together with co-ordination of effort.

In his second year, the medical student is beginning his contact with clinical medicine. In his course in military medicine, it is appropriate for him to begin to consider the professional details involved in provision of medical care in disaster relief. The scheme of evacuation of the patient from the catastrophe scene, with progressions of medical care from life saving to reconstruction and rehabilitative measures as he passes through the echelons of medical care, from the aid station, through the clearing station, to the evacuation and general hospitals, is developed. The modifications in this evacuation scheme, which brings definite treatment forward to the nontransportable patient, are discussed. The contrast with routine civilian professional care becomes manifest, in that professional service is rendered to a group rather than an individual patient and that this medical care is rendered by different groups of doctors rather than by one practitioner. Maintenance of teamwork requires administrative effort at various levels. This is discussed with respect to the intramedical integration, as well as the integration of the medical aspect with the total effort. The provision of medical supplies, when the drugstore and surgical-supply house are no longer available, becomes critical. The import of available supplies in the catastrophe situation, and the necessity for standardization, procurement, stockpiling and distribution and maintenance of equipment are considered. The value of standardized equipment is demonstrated by practical sessions in the application of triangular and roller bandages, and Thomas and other stock Army splint materials.

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This is combined with instruction in the practical first-aid measures that a second-year medical student should have in his armamentarium.

The catastrophe situation fosters the development of disease. In earlier wars the problems produced by disease and epidemic have exceeded medical capacity. In the last two years of the course, the advances of military preventive medicine that were successful in avoiding this eventuality in the recent war are presented. The methods that the Army has found of value in following the disease situation and in forestalling epidemics are discussed. Military preventive medicine encompasses all sanitary situations, from the most hazardous to the most salubrious, from the frozen Arctic to the tropical jungle. The student is indoctrinated with the basic principles involved in disease prevention and, guided by methods that have been found successful, is taught to improvise the solution fitting the particular situation in which he may find himself. The necessity and the means of enforcing the most rigid sanitary control in the catastrophe situation are stressed.

In these clinical years, while orthodox medicine, surgery and psychiatry are being presented, military medicine presents the modifications induced by the catastrophe situation. Therapy must be projected spatially as well as temporally. The teamwork impelled by the echelon system of medical care requires standardization of therapeutic procedure. Although the practice is repugnant to the traditionally individualistic physician, the welfare of the patient requires a limitation of procedures based on availability of equipment and personnel and the exigencies of the local situation. The concept of teamwork dictates that the plays be called in advance and that one man carry the ball just so far, passing it to his teammates who have been prepared to carry on. In medicine and surgery, the objective is the civilian ideal medical care. However, the disaster situation will often force the results to fall short of that objective, since masses rather than individuals are concerned, in the field rather than a scientifically designed operating theater. Still the recent war produced a medical record of which no member of the profession need be ashamed.

The psychiatric picture in the catastrophe situation is distorted by the disruption of normal habits, normal gratifications and psychic supports. The emotionally unstable may well be driven from the normalcy they cling to. The need for and value of preventive psychiatry and the feasibility of very early and mass therapeutic measures are demonstrated.

There are in addition unusual health hazards with which the military authorities are primarily concerned. Although diplomats may strive to eliminate the need, the medical profession must still be prepared to cope with the catastrophe produced by nuclear fission and chemical agents — a continual threat by accidents, industrial or diplomatic. The medical management of these situations is discussed in the fourth year.

It may be seen that the medical ROTC course today is primarily professional. This is consistent with current military planning, in which emphasis is placed on the professional qualities of medical personnel. However, the student who completes this course is to be qualified to assume the position of a commissioned officer in the Army. To this end, a minimum of time is devoted to give the future medical officer enough knowledge to avoid the embarrassment experienced by many medical officers who received their commissions with no military training and entered active duty with the relatively high rank conferred on all medical officers. The ROTC student is taught to recognize the grade insignia of personnel of the armed forces; he is also taught the principles of military courtesy and command and of military law. The basic principles of military correspondence and administration are explained, dispelling the physician's impression of "red-tape." He is given enough instruction in map reading to provide terrain appreciation and orientation — a knowledge of practical value.

As a potential member of the Army Medical Department, he is instructed in what it has to offer him. Its history and evolution to its present pattern and what it has contributed to the knowledge of medicine are discussed. Its research methods and plans, the part each person plays in contributing to the store of knowledge by keeping medical records is explained, and what the services offer as a medical career are discussed.

The history of this country shows that the medical profession has been outstanding in its patriotism. Traditionally the doctor is an "educated" man, not only professionally but also generally. However, the medical student of the current day has rarely the time to ponder the problems that confront the country. In the course in military medicine, three hours during each year are devoted to a discussion of the currently confusing and difficult problem of national and international affairs, reminding the student that, even while he is in medical school, he still has obligations to his country.

The medical ROTC program has completed its first year at Tufts College Medical School. Despite a student body composed largely of veterans, there has been a real and increasing response to the program. Student comment has indicated that the participants in the program concur in the practical value to be obtained from such a course. One third-year student wrote, "This course should be 'advertised' as essential to freshmen."

Present summer-camp attendance required of enrolled students consists of a six-week period of training at Fort Sam Houston, Texas, during which the material covered in the medical-school class-

room is actually demonstrated, and culminates in a field exercise in which the students participate in the evacuation and simulated field medical treatment. The many veterans among the current medical classes find this type of training reminiscent of unpleasant combat experience, and, although the objective is radically different, the similarity to previous experience suggests to them unnecessary repetition. There is discussion on the advisability of converting this summer training from field-type to professional-type training, during which the student will learn the administrative and technical factors involved in actual medical and surgical care of the Army sick and wounded.

Those who teach this course believe that the new physician who has completed a course in military medicine is that much better a physician. He is prepared to take a leading position in community defense plans; he is prepared to serve his country in or out of the armed force. He has demonstrated his willingness to make a sacrifice for the privilege of citizenship. It is possible that he will not be as adroit in litter drill as his father, but he is that much better a citizen and physician.

MEDICAL PROGRESS

ANTIBACTERIAL CHEMOTHERAPY (Continued)*

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Resistance

Priority for demonstration of the resistance of micro-organisms to specific drugs goes to Ehrlich,[153-155] who was able to isolate strains of trypanosomes resistant to three distinct drug classes. Resistance, in his experiments, was shown to arise by repeated passage through low concentrations in vitro or in vivo, to be permanent once established and to be specific for each class of drug. Thus, organisms made resistant to triphenylmethane dyes remained sensitive to azo dyes and organic arsenicals.

Ehrlich foresaw that drug fastness was to prove a major clinical stumbling block and proposed the only two means available for avoiding the difficulty: to eliminate *all* organisms as rapidly as possible; and to take advantage of the absence of cross-resistance by employing, when possible, drug combinations.[1,154] The same conclusions are, of course, repeatedly arrived at today from studies based upon a far more advanced understanding of the nature of resistance.

Resistance to the antibacterial chemotherapeutics was first encountered on an important clinical scale after a few years of sulfonamide treatment of gonorrhea.[156-159] A sharp drop in the cure rate was accompanied by the isolation of increasing numbers of sulfonamide-resistant gonococci.[160-163] Subsequent experience, both in the laboratory and in the clinic, showed that drug-fast organisms regularly developed when an initially sensitive strain was grown in the presence of an antibacterial drug. This was true with the sulfonamides and penicillin, but the most frequent and extreme cases of resistance occurred with streptomycin.[164-169]

Most workers are agreed that the development of resistance, like the chemotherapeutic action itself, is quite independent of the host. *It is not the patient but the bacteria that, under certain circumstances, become refractory to further chemotherapy.*

Resistance is encountered in two distinct forms. On the one hand a variety of bacterial species are relatively insensitive to the action of any one drug, and even among sensitive species more or less resistant strains are found. Detection of such resistant strains requires the use of very large inoculums, the drug then favoring survival of the less sensitive organisms.[170] One of the real disadvantages of streptomycin is the very wide range of sensitivity to its action displayed by organisms of every species.

On the other hand it has been frequently shown that resistant forms may arise *de novo* during contact of organism with drug. It was long an open question whether resistance of this kind arose through spontaneous mutation during the period of contact ("current mutation") or was to be attributed to a specific interaction of drug with bacteria. The outstanding work of Demerec[171] now appears to have settled the question in favor of the former hypothesis, at least for *Staphylococcus aureus* and *Escherichia coli*. Mutations occurring in random fashion give rise to resistant variants, which are then favored by selection in the presence of a drug. Resistance to penicillin and the sulfonamides proceeds stepwise with selection at each step to yield populations of higher and higher degrees of resistance.[78, 165] This is explained by the postulated presence of several genes, mutation of any one pro-

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ducing about the same degree of resistance and successive mutations producing additive effects. Since a double mutation would be an extremely improbable event, Step 1 mutants become predominant before a second mutation results in establishment of Step 2 mutants, and so on. With streptomycin, however, the stepwise character is by no means regular; variants of extremely high resistance may arise at once from a sensitive parent strain.[165, 166, 172] This fact is explained by the assumption that the several genetic factors vary in potency; since chance alone determines which will mutate, the result is an unpredictable irregularity in the degree of resistance. It follows that, with sulfonamides and penicillin, resistance can be controlled by reduction of the total number of growing organisms (since cell division favors mutation probability) to lower thereby the possibility of a Step 1 variant mutating again to Step 2. With streptomycin this is practically impossible since the first mutation of a sensitive organism *may* yield a highly resistant offspring. (A general review of the mutation problem was presented at the Cold Spring Harbor Symposium of 1946.[173])

Several investigators have shown that resistance only develops in actively growing populations,[164, 172, 174] as one would expect on theoretical grounds. One type of resistance to penicillin, characterized by production of penicillinase, may be increased *pari passu* with a rise in penicillinase activity, by rapid growth and frequent subculture in the absence of the drug.[174] Grown in ordinary mediums in the absence of penicillin, such resistant organisms do not revert, but when they are supplied with special substrates, reversion to the previously sensitive condition occurs.[102] It has never been shown that penicillinase meets the criterion for an adaptive enzyme, but exactly analogous findings regarding the appearance and disappearance of adaptive enzymes have been reported by Spiegelman and Reiner.[175] A theoretical approach to drug resistance, with emphasis on adaptation, is advanced by Hinshelwood,[176] and a conflicting point of view is presented by Sevag.[87]

A study of streptococci of groups A, B and C, grown in penicillin, reveals that one bacterial group may differ from another of the same species, in the tendency to become drug-fast, the characteristics of the resistant forms and the permanence of resistance.[177] Resistant organisms arising through current mutation sometimes show a surprising tendency to revert upon removal of the drug[101]; this is difficult to explain on a basis of back-mutation unless it can be shown why nonresistant forms would be favored in the absence of drug. The only evidence bearing on this is the finding that certain resistant strains have a slower growth and metabolic activity than the parent sensitive strain.[78, 104]

Except for the unique case of penicillinase-producing organisms, it is now generally accepted that bacteria become drug-resistant by developing an alternate metabolic pathway, which by-passes the previously inhibited steps. How this could occur on a mutation basis is indicated by the fundamental studies of Beadle and his collaborators,[181] who showed that the presence or absence of the enzyme mediating each metabolic step in Neurospora is controlled by a single gene. Appearance of a new enzymatic step circumventing that inhibited by a drug might thus arise from random gene mutations. Of unusual interest in this connection is the report of a Neurospora variant requiring sulfonamide for growth and inhibited competitively by PABA.[178]

From the clinical standpoint the resistance problem offers the greatest drawback to the use of streptomycin. It has been shown repeatedly that organisms cultured from refractory patients after prolonged therapy prove resistant as compared with the original strain and that this development may occur with alarming rapidity,[179-184] often carrying a disease quickly beyond control by the drug. This emphasizes the importance of frequently determining organism sensitivity and, so far as possible, increasing dosage to meet new thresholds.

If the concepts outlined above are correct there seems no sure method of avoiding drug fastness. "Frapper fort et frapper vite!"[71] remains the only countermeasure. Mutation to resistance is unlikely to occur if multiplication of organisms can be stopped at once, and variants beyond the first step will almost certainly not appear. Prompt treatment with adequate dosage until an infection is entirely eliminated offers the best hope of control. Combined medication, suggested by some authors[185] and yet not generally employed, seems thoroughly logical since the few variants resistant to one agent can be controlled by the other before selection makes them the predominant type.

The appearance of streptomycin-requiring organisms has been reported by several investigators.[186-190] These were avirulent for animals until streptomycin was administered, when fatal infection promptly ensued. Although it is not inconceivable that these facts may have clinical significance, the results cited were obtained in vitro, and no authenticated case of therapeutic failure on this basis has yet been reported.

Toxicity

It is axiomatic that an effective chemotherapeutic is a compound of low toxicity that has shown a favorable chemotherapeutic ratio in experimental animals. Toxicity, broadly speaking, is of two kinds: one bears a definite relation to dosage; the other falls into the category of sensitivity phenomena, whose incidence and severity do not strictly depend upon the amount of drug administered. Either type may appear after brief or prolonged exposure to a drug. Acute reactions of the first kind are generally elicited in toxicity tests with

small animals (such as the mouse intravenous LD_{50}); chronic reactions are brought out by prolonged feeding or repeated injection into a variety of animals. Molitor's[191, 192] report on streptomycin is a classic study of acute and chronic toxicity in animals.

Unfortunately, as Marshall[193] points out, although animal toxicity may in a general way resemble effects in human beings, the correlation is by no means reliable, and toxic dosage, expressed in milligrams per kilogram, can rarely be translated from species to species. The wartime antimalarial program[194] brought this out for a considerable number and variety of drugs. Furthermore, reactions of the sensitivity type often cause the greatest difficulty in the clinic, and yet these are rarely observed in experimental animals. Caution is therefore necessary in the prediction of human toxicity from animal experimentation alone, although without question major toxic potentialities will be revealed in such studies.

Sulfonamides. Sulfonamides display a variety of untoward effects, manifested by sulfadiazine and sulfamerazine to a lesser degree than by some of the earlier members of this group. These have been fully discussed by Janeway.[195, 196] The major toxic manifestations of sulfathiazole, sulfadiazine and sulfamerazine are damage to the kidneys, interference with the normal production of leukocytes, and fever. The last two are evidently sensitivity phenomena, unpredictable, and often elicited by extremely small doses. The prevention of granulopenia has not been achieved, but the gravity of this condition has been considerably minimized by prophylactic control of secondary infection with penicillin.

The twofold effect upon the kidneys (crystalluria and toxic nephrosis) is closely dependent upon the drug dosage and certain other important factors. Crystalluria has long been recognized as a simple consequence of supersaturation of the urine, where these drugs and their acetylated derivatives are highly concentrated. All become increasingly soluble at an alkaline pH, a fact that provides the rationale for adjuvant alkalization, forcing of fluids to permit excretion of a reasonably dilute urine and frequent check on the urine pH and specific gravity. An interesting approach to this problem was proposed by Lehr[197] and also by Frisk and his co-workers,[198] who demonstrated that, as theory predicted, the solubility of one sulfonamide is almost independent of others present in the same solution — for example, a saturated solution of sulfathiazole will dissolve nearly as much sulfadiazine as an equal volume of water. It had long been known that most of the sulfonamides act similarly, and more or less additively against sensitive microorganisms. These facts are the basis of the suggestion that mixtures of sulfonamides invariably be employed, whereby the total dose is divided among three drugs. The mixture employed by Frisk, with significant reduction in crystalluria, consisted of sulfathiazole, sulfadiazine and sulfamerazine in the proportions 37:37:26. Larger doses could be given and higher blood levels (of total sulfonamides) attained than otherwise, without supersaturating the urine with any of the three compounds or their acetyl conjugates. Whereas crystalluria is unquestionably reduced in experimental animals,[199] and in some clinical experiences,[200] conflicting clinical reports have appeared.[201] One might raise the question whether it is wise to risk sensitizing patients to three drugs instead of one in view of the fact that patients reacting to sulfathiazole, for example, often tolerate sulfadiazine or sulfamerazine. Whether from the standpoint of over-all toxicity the use of mixtures is in fact superior to single-drug regimes remains to be proved in a statistically valid number of patients.

It is not clear whether the toxic nephrosis occasionally seen is closely related to the crystalluria, but, curiously enough, alkalization of the urine reduces the incidence of both.[202]

Penicillin. Penicillin remains a pharmacologic curiosity because of its almost completely innocuous character. No toxic effects of the dose-related type have been reported; this is the more remarkable in view of the enormous number of persons (literally millions) who have received the drug. The lethal dose of penicillin cannot be determined since it is less toxic than any of the cations (sodium, potassium, calcium and so forth) with which it has been associated.[203, 204] Doses of several million units daily are regularly tolerated in the treatment of refractory diseases, but it must be observed that the "enormous" dose of 10,000,000 units daily represents only 6 gm. of penicillin G sodium, and only 0.5 gm. of the cation. On the other hand intrathecal injection may, and direct cortical application does, lead to convulsive phenomena of unknown mechanism with both penicillin[205] and streptomycin.[206]

Sensitivity reactions occur in about 5 per cent of patients, usually as urticaria (which responds to antihistaminic drugs), dermatitis or drug fever.[61, 207-211] These appear most frequently with oil-and-wax mixtures, which are also prone to cause annoying local tissue reactions.[212-214]

Streptomycin. Streptomycin, unfortunately, displays a serious toxic effect of the dose-related type — that upon the eighth nerve and vestibular apparatus.[215-218]

The relative infrequency of this injury in the therapy of acute infections suggests that duration of therapy (or total dose) is the crucial factor. The statistical incidence of the reaction is not easily assessed, since it often appears in mild and reversible form as a disturbance of hearing or equilibrium that may not be especially prominent while patients are bed ridden.[215] Moreover, a number of the reported cases occurred in persons suffering from

infectious disease of the central nervous system so that the drug could not surely be implicated. In any event the tendency has been, when possible, to avoid administering streptomycin for longer than a few weeks.[219] In the treatment of chronic infections analogy to the arsenicals might suggest rest periods, but this is illogical because it would favor the development of drug resistance. The problem appears to lack a practical solution, the nature of the remarkable specific affinity for a particular group of nerve cells[220] is not understood, and the clinician is left little choice but to weigh the risk of prolonged treatment against its possible value and to warn the patient of the hazard.

In the therapy of urinary-tract infection, which constitutes one of the major indications for streptomycin, advantage should be taken of the enhanced potency of the drug in alkaline solution; chemotherapy should be preceded and accompanied by alkalization procedures.[221] By increasing the potency of each microgram of streptomycin excreted into the urine one is enabled to reduce the systemic dosage to a point where the dangers of toxicity are distinctly lessened.

The use of streptomycin is also attended by the usual variety of sensitivity reactions,[218] including contact dermatitis among physicians and nurses who handle it frequently.[222, 223] Sensitivity may be ascertained by patch tests or intradermal inoculation; caution is indicated in the latter procedure by the report of a recent nearly fatal case in a hypersensitive person.[224] One might observe that sensitivity reactions to drugs in general are among the least understood subjects in pharmacology. Though neglected in the past, they comprise a potentially fruitful field for joint study by pharmacologist, immunologist, physical chemist and clinician.

Pharmacodynamics

Question of Drug Levels

It is generally agreed that the practical aim of chemotherapy is to administer a drug in such a way that optimal in vitro concentration will be maintained at the locus of infection, continuously and until infectious organisms are entirely eradicated. This implies that all measures employed will be designed to maintain an effective drug level in close contact with the bacterial cells.

Recently the importance of drug levels, especially in the plasma, has been questioned, particularly by Marshall.[193] That certain infections can be cured despite undetectable or negligible blood levels is undeniable, especially with drugs that are selectively taken up or irreversibly bound by parasite or tissue proteins. In the arsenic-bismuth treatment of syphilis, for example, cure is more dependent on total dose than on concentration, and the frequency of administration is not highly critical.[225, 226] Likewise, in antimalarial therapy, some drugs are so highly concentrated in certain tissues that plasma levels are insignificant by comparison[194]; yet even with quinacrine, which has a high tissue-plasma ratio, Shannon[227] found good correlation between plasma levels and clinical response. Certainly, no generalization will apply to all drugs; the question here is to what extent plasma drug levels are important in antibacterial chemotherapy.

Little doubt has been expressed that the sulfonamides act at a definite threshold concentration determined by the sensitivity of each bacterial strain and species, and the same observation is true of the *bacteriostatic* action of penicillin and streptomycin. Eagle and Musselman[72, 228] recently demonstrated a paradoxical effect whereby certain streptococci and staphylococci show a *decreased death rate in vitro* at very high penicillin concentrations. It was suggested that too much penicillin might prove harmful in infections caused by these organisms. However, the clinical importance of the "paradoxical phenomenon" can be questioned, since bacterial growth is presumably inhibited through the whole range of concentrations in which the paradoxical *bactericidal* effects are observed.

Some early workers cited the increased sensitivity of growing cells to the killing action of penicillin as a rationale for giving the drug intermittently; levels would fall repeatedly, and the bacteria would enjoy brief periods of growth, during which they would again be subject to the bactericidal effect of the drug. Here again, the importance of bacteriostatic action was overlooked. To release a dangerous pathogen from effective growth inhibition so that it can multiply and be killed is like releasing a petty criminal from jail in the hope that he will commit murder and become subject to electrocution.

Actually, the argument was *post hoc* reasoning in an attempt to explain why intermittent injection, with zero plasma levels for about half the time, was so outstandingly successful in the control of clinical infection. It has been shown that organisms removed from exposure to penicillin do not actually resume growth for several hours[74-76] — a fact that goes far to explain the efficiency of an intermittent schedule.

Sweeping generalizations are sometimes made on the basis of the fact that in animal or human infection it is often possible to reduce the frequency of administration of a chemotherapeutic without loss of efficiency. For example, pneumococcal and other infections in mice have been cured by a single large dose of penicillin in place of repeated smaller doses.[229, 230] Similarly, guinea pigs can be protected against lethal tuberculous infection if streptomycin is administered as a 25-mg. dose, whether that amount is given daily, or once in five days.[231] In a well designed experiment[232] rats were protected

against infection when the animals were injected with pneumococci *after disappearance* of detectable plasma levels following a single dose of penicillin. This result may be explained in part by the recent findings[233, 234] that penicillin levels in tissues and lymph persist for some time after plasma levels have disappeared.

In human beings gonorrhea has been cured by a single 15-mg. dose of penicillin,[235] and prevented by the single prophylactic administration of 1 or 2 gm. of sulfathiazole.[236] The meningococcus carrier state can be eradicated by a single dose of sulfadiazine.[237]

These observations must all be interpreted in relation to the duration of levels after the single

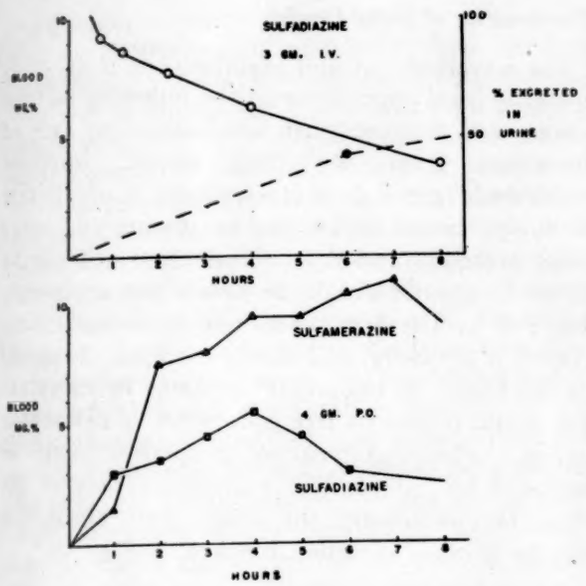

FIGURE 4.
The upper half shows blood levels (solid curve) and cumulative urinary execretion (broken curve) of sulfadiazine after single intravenous administration (data of Sadusk and Tredway[238]). The lower half shows blood levels of sulfadiazine and sulfamerazine after single oral administration (data of Bullowa and Ratish[239]).

dose, the threshold level for the organism concerned and the response of the organism to varying periods of exposure to the drug. Every "single dose" is in reality a *course of treatment*, in which the pathogens are exposed to a changing drug level for a definite period (Fig. 4-6). Increasing the size of the single dose not only raises the peak level but also prolongs the duration of suprathreshold concentrations. If an infection can be cured by short exposure of pathogens to a low drug concentration, effective cures will also, of course, be obtained through a wide range of higher doses and longer exposures. The experiments cited, then, represent a critical testing of the minimal requirements for cure, in infections caused by highly sensitive organisms.

Refractory infections provide a more exacting test of the limits within which dose and frequency can be varied. In the treatment of subacute bacterial endocarditis, Loewe[242] reports that patients who fail to respond to prolonged therapy by the

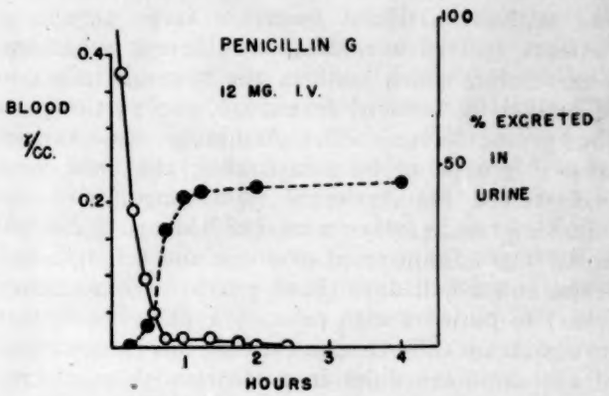

FIGURE 5. *Blood Levels (Solid Curve) and Cumulative Urinary Excretion (Broken Curve) of Penicillin G after Single Intravenous Administration (Adapted from Data of Rammelkamp and Keefer[240]).*

continuous route at a constant plasma level may be cured when the plasma penicillin level is raised. Priest and his collaborators[243] also stress the importance of high and constantly maintained plasma levels in the management of this disease.

The fundamental studies of Eagle and his associates[244] on time-dose relations in the cure of rabbit syphilis, demonstrate clearly that therapeutic efficiency depends upon maintenance of an effective blood penicillin level for a specified period of time.

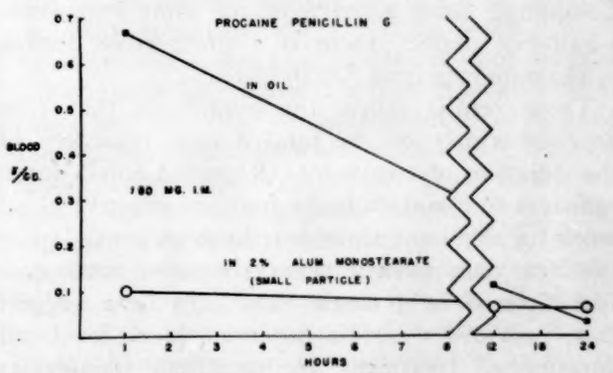

FIGURE 6. *Penicillin Blood Levels after Single Intramuscular Administration of Two New Repository Products (Data of Thomas et al.[241]).*

The dose curing half the animals (CD_{50}) was lowest when repeated injections of small amounts of penicillin were given for a long time. The lowest CD_{50} was 360 units per kilogram of body weight, given as fifty injections (7.2 units per kilogram each) at

four-hour intervals. Increasing or decreasing the interval, or reducing the number of injections with the same interval, had the effect of raising the CD_{50} — that is, more penicillin was required for cure.

The clinical counterpart of these studies is embodied in the report of Schwemlein et al.[245] on the results of penicillin therapy of syphilis, with and without artificial fever, in large groups of patients treated according to different schedules. The results, which confirm the synergistic action of artificially induced fever, are also pertinent to the present discussion. Assuming the various treated groups to be comparable, the data have been tested for statistical significance, with the following results: when a total of 720 mg. (1,200,000 units) was administered over one and a fourth and seven and a half days (both groups with accessory fever) to patients with primary syphilis, there was no significant difference in the cure rate; comparison of the same schedules in patients with secondary or relapsing syphilis gave a marked advantage to the longer schedule. It is obvious, as had previously been recognized, that early syphilis responds more easily than the longer established types. In such easily eradicated infections both the dose and the duration of treatment were probably more than adequate even in the one-and-a-fourth-day schedule.

Examining the combined cure rates for primary, secondary and relapsing cases, one finds that the 720-mg. schedule is equally effective whether spread over seven and a half or three and three-fourths days but produces fewer cures when the length of treatment is cut to one and a fourth days. Furthermore, although 15 gm. is more effective than 6 gm. given in a single day, it is distinctly less curative than 720 mg. over three and three-fourths days. Comparing doses given over the same seven-and-a-half-day period, there is a progressive decline in the cure rate from 720 to 180 mg.

These results refute the hypothesis that cure depends largely on the total dosage, regardless of the duration of treatment. Repeated small doses, sufficient to maintain fairly constant effective blood levels for three and three-fourths days, proved more effective than twenty times the same total dose administered in a single day. The data suggest that, provided a certain minimum blood level and duration of treatment are exceeded, treponemas can be reliably eradicated within a considerable range of reciprocal variation in both these factors.

Critical re-examination of the need for constant plasma levels has contributed to knowledge of actual minimum chemotherapeutic requirements in human disease. This is especially important in the use of streptomycin, excessive administration of which causes an unnecessarily high incidence of toxicity. This drug may be given less frequently and in shorter courses than had been thought necessary without reduction of cure rate in a number of infections.[219]

Nevertheless a wholly negative attitude toward plasma levels does not seem justified. The whole body of in vitro evidence showing the intimate dependence of growth-inhibition and killing rates upon drug concentration cannot be dismissed; nor should the established dangers of inadequate levels be overlooked in the search for the dosage schedule that will just exactly cure. Unless the immediate environment of the pathogenic organisms can be sampled (as in the urinary-tract infections) the plasma level remains the only indication of the probable drug concentration to which they are exposed.

Maintenance of Drug Levels

The establishment and maintenance of an effective drug level depends upon the following factors: dosage, and frequency of administration; rate of absorption from the drug depot, wherever established; rate of drug inactivation, if any, within the body; extent of binding to plasma and other tissue proteins; and rate of excretion. Ideally, a chemotherapeutic should be slowly but completely absorbed by the oral route, not appreciably inactivated in the body, and slowly excreted. It should not be bound to nontarget* proteins to an extent that would reduce its free concentration below that desired. Pharmacodynamic properties may be improved by independent variation of any of the above factors toward the ideal; thus, absorption may be slowed, excretion blocked, and so on.

Sulfonamides

The sulfonamides present no serious pharmacodynamic problems. Sulfamerazine comes close to the ideal in all respects, oral administration of a 1-gm. maintenance dose every six to eight hours proving adequate to maintain a fairly constant bacteriostatic level of the order of 8 mg. per 100 cc., and sulfadiazine, requiring ingestion every four or six hours, is not inconvenient, although levels will fall during the night if medication is stopped. Large priming doses are needed with all the sulfonamides to establish a higher plateau level than could be reached by simple repetition of the maintenance dose from the start.[195, 238, 239, 246-250] Figure 4 shows (upper portion) the rate of disappearance of sulfadiazine from the plasma after *intravenous* administration and its simultaneous appearance in the urine. The lower portion of Figure 4 shows the typical course of the plasma-level curves for sul-

*Proteins of various tissues, including the plasma, in contradistinction to those of the parasite.

fadiazine and sulfamerazine after *oral* administration.

High local concentrations in the gastrointestinal tract are made possible through molecular modifications resulting in decreased absorption (sulfaguanidine and sulfathiadiazole[251]) or very slow release of active drug (sulfasuxidine and sulfathalidine). High levels for combating localized infection in the urinary tract are automatic, so to speak, even when dosage is small and blood concentrations low, by virtue of the quantitative excretion of these drugs by the kidneys. A number of new sulfonamides have been investigated,[252-255] and some whose chief virtue is high solubility have been tested in the clinic.[256, 257]

Penicillin

Penicillin presents the problem of poor absorption by mouth, rapid absorption from intramuscular depots and an extremely rapid renal excretion, resulting in fluctuating levels with high peaks and deep valleys.[240, 258, 259] Figure 5 illustrates the rapid disappearance of penicillin from the plasma after intravenous administration and its simultaneous appearance in the urine. To overcome these serious deficiencies and devise some means of maintaining fairly constant levels with a modicum of comfort to the patients has been the aim of considerable research. It was early shown that oral administration of three to five times the usual intramuscular dose would yield comparable levels.[260, 261] The belief that gastric acidity was largely responsible for inactivation by the oral route has been generally discarded for lack of evidence,[262] and simple administration every three hours of at least 60 mg. (100,000 units) by tablet proves effective, though uneconomical. Results of treatment by this route of several hundred cases of gonorrhea compared favorably with those generally obtained when penicillin is given intramuscularly.[260] The oral route, however, is contraindicated in the treatment of serious infections because absorption is, at best, irregular and unpredictable.

Early efforts were directed toward slowing absorption from an intramuscular depot by such crude means as chilling the site or injecting epinephrine, but the first method generally employed was the intramuscular injection of a large amount of penicillin in a mixture of peanut oil and beeswax (Romansky).[263] A single dose of 180 mg. (300,000 units) produces detectable levels for as long as twenty-four hours.[264] The injections, however, may be painful and lead to a higher incidence of local and allergic reactions than with aqueous solutions.[212]

The principle embodied in the peanut-oil-beeswax mixtures has led to the development of several other so-called "repository" products.[265, 266] Loewe[267] obtained results that compared favorably with the Romansky formula, using a water-soluble preparation of penicillin in gelatin and dextrose. It was reported that a large number of insoluble metallic salts of penicillin released the active drug at a slow rate from intramuscular depots,[268] and complexes with cationic dyes had the same effect. A compound consisting of a mol of penicillin combined with a mol of procaine was shown to act similarly. This material, which is now on the market in several forms, when suspended in an oily vehicle, was shown to produce detectable levels for longer, and in a higher proportion of patients, than the Romansky formula.[269, 270] Herrell and his associates, [271, 272] employing procaine penicillin suspended in sesame oil, report reliable prolongation of levels up to thirty hours after a single 180-mg. (300,000 units) injection. These investigators express the view that the procaine confers an anesthetic effect[273] and also, presumably, an antihistaminic one, since allergic reactions are so rare, even among patients previously reacting to ordinary penicillin. Similar results have been obtained by other workers,[274] with aqueous suspensions of procaine penicillin. In a well controlled study of six repository products, Thomas and his collaborators[241] have shown that the most favorable results are obtained with procaine penicillin in peanut oil with aluminum monostearate. The particle size is critical, a striking advantage of 5-micron over 50-micron particles being observed. With the small particle size a single injection of 180 mg. resulted in levels above 0.018 microgm. (0.03 units) per cubic centimeter in 86.7 per cent of the subjects after four days. Figure 6 shows the markedly prolonged plasma levels resulting from the single administration of two different repository preparations by the intramuscular route.

It should be clear that the repository method will be satisfactory for the treatment of infections requiring relatively low penicillin levels. Unfortunately, the stress that is placed upon duration of detectable levels directs attention away from the shape and height of the plasma-level curve during the whole period between injections. With the earlier repository preparations peak levels were rather low so that in grave infection requiring a high penicillin level it was more reliable to depend upon intermittent aqueous injections or continuous intramuscular or intravenous infusion. The latter method carried with it the difficulty of local phlebothrombosis, but the assurance of an unvarying, high plasma level.[275] Thrombosis is attributed to thromboplastic effects of the drug in vitro,[276] but this has been disputed.[277] It is too early to say whether the favorable properties of the newer repository preparations will allow one to establish and maintain *high* constant levels, but this seems a likely possibility.

In the treatment of localized infections much may be gained from a local drug level higher than would result from simple equilibrium with the

plasma. Such levels can be established in infections of the skin,[278] oral and other mucous membranes,[279] paranasal sinuses, pulmonary tree, and other sites, by direct topical application. An interesting development along these lines is the use of aerosol or dust inhalations of small-particle size in the treatment of pulmonary, tracheobronchial and sinus infections.[280-286] Concentrations thus established in the pulmonary tissues of animals are several times higher than those in the plasma.[287] On the other hand the finding of definite plasma levels after aerosol or dust therapy qualifies the method as a convenient and generally useful one in systemic penicillin therapy. High drug concentrations in the urine are again attained willy-nilly as a consequence of the rapid quantitative excretion of penicillin by the kidneys.

Another approach to the maintenance of constant plasma levels has taken the obvious direction of attempts to slow the renal excretion of penicillin. The renal plasma clearance is found to be between 755 and 1120 cc. per minute,[275] and by another investigator[288] about 560 cc. per minute, figures that approximate the total blood flow through the kidney. These values are to be compared with 12 to 34 cc. per minute for sulfadiazine and 4 cc. for sulfamerazine.[289] Thus, about 80 per cent of penicillin excretion is via the tubules, a fact that early suggested that other tubule-excreted compounds might act as blocking agents. Benzoate (excreted as hippuric acid), p-amino-hippuric acid and diodrast have all been shown to diminish the clearance of penicillin and thereby to raise the average plasma level.[290, 291] Water and salt restriction enhance this effect,[292] presumably by diminishing the effective renal blood flow; combinations of these methods have succeeded, somewhat irregularly, in increasing plasma levels as much as fourfold to eightfold. However, fluid restriction seems undesirable in febrile infections, and some of the compounds employed are not wholly innocuous.

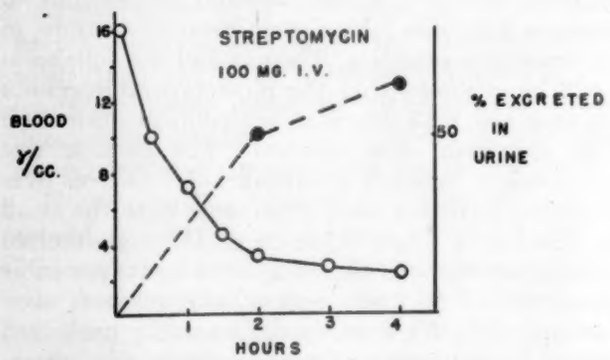

FIGURE 7. *Blood Levels (Solid Curve) and Cumulative Urinary Excretion (Broken Curve) of Streptomycin after Single Intravenous Administration (Adapted from Data of Adcock and Hettig[305]).*

A more subtle method made its appearance with the discovery by Beyer and his associates[293] that a sulfone compound, 4′-carboxyphenylmethanesulfonanilide (caronamide), blocked the tubular excretion of penicillin, reducing plasma clearance to the glomerular rate. The substance interferes with the tubular transport mechanism but does not affect the clearance of a variety of compounds excreted by glomerular filtration.[294] Caronamide itself, although it acts specifically upon the tubules, is excreted solely by the glomeruli.[295] Clinical experience has shown that ingestion of 2 to 4 gm. every three hours is well tolerated by most patients. No case of severe toxicity has been reported,[296] although gastric intolerance occurs not infrequently.[291] The average penicillin plasma level is raised twofold to sevenfold; the duration of detectable levels after a single intramuscular dose of penicillin is appreciably extended; and in general the response to 60 mg. (100,000 units) of penicillin approximates that usually seen to 180 mg.[291, 297] In aged persons the normal clearance of penicillin is below the average, and caronamide is effective in smaller doses than in younger subjects.[297]

The great concern about rapid loss of penicillin in the urine originated in the days when the drug was scarce and dosage had to be minimal. The tendency in many clinics today is toward use of very much larger routine doses than had been originally recommended. Should the new repository preparations fulfill their present promise it is quite possible that adequate .control of most infections will be achieved by proper choice of the interval at which large doses of such preparations are injected. The use of adjuvant medication of the caronamide type would then be rendered unnecessary.

Streptomycin

From the pharmacodynamic standpoint the properties of streptomycin lie midway between those of the sulfonamides and penicillin. It is practically unabsorbed by the oral route but is not destroyed in the gastrointestinal tract[298, 299]; the convenient route for systemic therapy is thus barred, but employment against enteric pathogens is made possible.[300, 301] When the drug is administered intramuscularly the plasma-level curve falls more slowly than that of penicillin, the slow fall being related to the low renal clearance of 30 to 80 cc. per minute.[299, 302, 303-305] The declining slope of the plasma-level curve indicates a permissible interval of four to six hours between doses. Figure 7 shows the disappearance of streptomycin from the plasma and its appearance in the urine after intravenous administration. An interesting mathematical treatment enabling one to predict plasma-level and time relations with remarkable accuracy, not only for streptomycin but also for other drugs, has been

formulated by Boxer and his co-workers.[306] With streptomycin the wide variation in thresholds of different organisms, and the real importance of maintaining effective levels to combat the threat of drug fastness should dictate a flexibility of dosage and interval based upon expected levels and checked frequently in each patient.

The various methods of topical administration for high local concentrations are just as applicable here as with penicillin. In addition very large doses may be given by mouth in the treatment of intestinal disease caused by gram-negative bacteria or for preoperative sterilization of the bowel.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 35041

PRESENTATION OF CASE

A forty-six-year-old masseur was admitted to to the hospital complaining of intermittent fever.

Four months before admission he developed bronchopneumonia and was ill for about three weeks, with a temperature up to 102°F., moderate cough without bloody sputum and slight diarrhea. He received sulfadiazine for one week without benefit and then penicillin. While he was on the latter therapy the course slowly improved. He became asymptomatic during the next few weeks but was unable to regain the 25 pounds he had lost during the acute illness. There was a marked change in his muscular appearance, with definite atrophy, particularly of the muscles of the arms and shoulders. Two and a half months before admission he noted listlessness, easy fatigability and an afternoon temperature to 100.5°F., followed by profuse sweating. There were no night sweats, cough or pain. Febrile rises occurred periodically.

He had had nocturia (twice a night) for many years. The patient's wife stated that he had frequent nausea, vomiting and chest pain. For about five years he had been troubled by migratory arthralgias. On several occasions he had periarticular swelling of the hands and knees, suggesting urticaria. The arthralgias were readily relieved by aspirin, and medical aid was not sought.

Physical examination was negative except for slight pallor.

The temperature was 99°F., the pulse 100, and the respirations 20. The blood pressure was 132 systolic, 82 diastolic.

Examination of the blood disclosed a white-cell count of 8600, with 73 per cent neutrophils, 22 per cent lymphocytes, 1 per cent mononuclears and 4 per cent eosinophils. The hemoglobin was 11.8 gm. The specific gravity of the urine ranged between 1.002 and 1.006, with a +++ or ++++ test for albumin. On microscopical examination occasional red and white cells and granular, cellular and hyaline casts were found in the sediment.

The sedimentation rate was 13 mm. in one hour. The nonprotein nitrogen was 18 mg., the calcium 8.8 mg. and the phosphorus 3.3 mg. per 100 cc. The alkaline phosphatase was 3.7 units. A cephalin flocculation test was + in twenty-four and ++ in forty-eight hours. The total protein was 6.95 gm., with an albumin-globulin ratio of 1.18. Blood cultures were negative. The brucellergen skin test was negative. Tuberculin (O.T.) was positive in dilution of 1:100 in twenty-four hours, with a 3-cm. to 4-cm. area of erythema and induration and some pruritus. An electrocardiogram was normal. The basal metabolic rate was + 10 per cent.

An x-ray film of the chest was normal. A film of the left knee showed slight hypertrophic changes about the articular surfaces consistent with a slight degree of osteoarthritis. On Graham test the gall bladder filled with well concentrated dye and contained a rounded, nonopaque shadow consistent with calculus. A gastrointestinal series demonstrated a constant narrowing in the prepyloric region for a distance of 3 cm. In the center of the narrowed portion a constant collection of barium,

measuring 1 cm. in diameter, was seen. A plain film of the abdomen demonstrated that the right renal shadow was larger than the left.

The hospital course was essentially afebrile, and the patient was discharged seven days after admission. A short time later he was admitted to another hospital, where x-ray studies failed to demonstrate the prepyloric lesion previously found. An intravenous pyelogram and gastric analysis were negative. A gastrointestinal series one month later suggested a duodenal ulcer, with spasm of the antrum. Following discharge the course at home consisted of rather persistent fever and fleeting severe joint pains. There were no objective joint changes, however. Weight loss was progressive. Bloody diarrhea, persistent vomiting and oliguria appeared. He did not become comatose. Joint pains and fever continued up to the end. He died about one month after leaving the hospital.

Differential Diagnosis

Dr. William W. Beckman: The tuberculin test was positive in dilution of 1:100. I assume that it was negative in higher dilutions.

Dr. Tracy B. Mallory: I do not believe we know.

Dr. Beckman: Obviously I do not know what this man had. If one reads the present illness, the past history and the routine laboratory work and sets them apart from the rest of the record, one has a history of five years' nocturia (twice a night), and a few months of anemia, albuminuria and pallor, symptoms that seem to have been precipitated by acute infection, and one forms the first impression that this patient was suffering from exacerbation of underlying nephritis, precipitated by acute infection. When one goes on a little further to try to distinguish the nature of the renal disease (I am sure that he must have had some kind of renal disease), it becomes less clear what kind it was. He obviously had some diffuse constitutional disease that gave rise to fever, weight loss, general malaise and so forth. That could be part of the nephritis, although fever is an unusual symptom in that disease. He also seemed to have had some kind of skeletal disease. The changes in his muscular system did not prove as striking on physical examination as one would have expected on reading the history. At any rate, he had some kind of disease that gave him joint pains off and on in the past and ultimately during the final illness were an important feature. Apparently in this hospital no one saw objective signs of joint disease; at least, there is no record. I do not see how one can make a definite diagnosis of the type of joint disease. I suppose we can say that it was consistent with rheumatoid arthritis, but that means nothing. Perhaps the x-ray films will help us decide what the osteoarthritis is. We do not know what symptoms led to the taking of the gastrointestinal series, but there was some abnormality. Of course, he did have diarrhea and later bloody diarrhea.

Dr. Stanley M. Wyman: I did not plan to show this film. It is not a very impressive picture of arthritis.

Dr. Beckman: It certainly is not — probably normal knees.

Dr. Wyman: The films of the chest show questionable diminution in size of the right middle lobe and some increased linear markings, consistent with an old, chronic process with fibrosis. The lung fields are otherwise clear. The heart shadow is not remarkable for a patient of this age. The findings in the gastrointestinal tract as recorded by these films consist of an area of narrowing in the prepyloric and distal antral region; it is seen on all the films. This area on a second examination appears to contain a crater measuring perhaps 1 cm. in diameter. The gall bladder shows a small, round, radiolucent shadow consistently on four separate films. The spleen may possibly be a little larger than usual. The right kidney is of normal contour. The left kidney is partially obscured by barium but appears smaller than normal, much like a shrunken kidney. I can see no unusual areas of calcification, no unusual masses and no evidence of destruction of bone.

Dr. Beckman: I suppose at least we can make the diagnosis of a gallstone, but that hardly seems to explain the situation.

This patient had three distinct systems — renal, circulatory and gastrointestinal — involved in this disease, and I suppose the object of this discussion is to try to think of ways in which one can explain most of the symptoms — not all of them — by one diagnosis. I do not know that I can. When one reads the history of the present illness, one thinks of chronic nephritis, but the lack of any nitrogen retention is very much against that. Chronic pyelonephritis or chronic glomerulonephritis would not cause as many symptoms as this did. So I do not believe that either of those diagnoses need be entertained too seriously. I do not know how one can absolutely rule them out, although I would expect nitrogen retention if the patient was as sick as this from chronic pyelonephritis or chronic glomerulonephritis. One has to give consideration to the fact that at the onset of the illness he had received sulfonamides, which are known to cause a type of renal lesion. Dr. Mallory has taught us to believe lower-nephron nephrosis is reversible so one would anticipate that the patient would either have died sooner or have been better by this time.

I was interested in the x-ray film of the knees because I thought if the patient had rheumatoid arthritis, one would have to entertain the possibility of amyloid disease, which is frequently a complication of rheumatoid arthritis and in which some people say, at any rate, albuminuria and other evidence of renal disease can occur without much

nitrogen retention and without high blood pressure. This man did not have high blood pressure in the one recording we have. I have no way of ruling out amyloid disease. It would explain a number of the symptoms and possibly the fact that the spleen was in the upper limits of normal by x-ray study, even if not palpable. There is no way to establish that diagnosis, however; it is just something one mentions tentatively.

Of course there is always periarteritis nodosa to be thought of with this sort of symptomatology. It produces gastrointestinal symptoms, skeletal symptoms and renal disease. It has many different kinds of manifestations, and I do not see how one can make the diagnosis clinically, unless there is asthma or a high eosinophil count in conjunction with these symptoms. In 1939, when Dr. Short was making out the diagnostic file for the Arthritis Clinic, a great many routine records were reviewed and it was decided that an eosinophil count of 4 per cent was the upper limit of normal. The pulmonary disease in this case was acute infection, not asthma. Perhaps some of the findings seen in the x-ray film are the result of periarteritis nodosa; I do not know. There is no way of establishing it or ruling it out, but it would explain all the symptoms.

Someone obviously thought of undulant fever as a possibility. One of my students just told me that he thought that that was the diagnosis in this case because all the symptoms that this patient had have been ascribed to undulant fever. Considering how often the brucellergen skin test is nonspecifically positive, I would be unwilling to make the diagnosis in the face of a negative test. I doubt if all the things ascribed to undulant fever are due to it.

The most likely bet that I can make is that the patient had periarteritis nodosa. I am puzzled by the terminal bloody diarrhea, which suggests ulcerative colitis more than anything else, and also because of the fact that he had diarrhea at the onset of the illness. That is not usually a feature of periarteritis. I am at a loss to explain that. It is possible that he had ulcerative colitis as a terminal event; it sometimes happens. As I have said, beyond making the diagnosis of gallstones that show up by x-ray study, I have to speculate about the rest. Certainly he had a generalized constitutional disease that involved the kidneys, joints and gastrointestinal tract, and periarteritis nodosa would explain it.

Dr. Walter S. Burrage: There are one or two points of interest not clearly brought out in the history. The patient had severe joint symptoms early in the game. He went to his place of occupation from his home on quite a number of occasions when he had to have crutches and be assisted in and out of the bus by the bus driver. The joint symptoms in the feet, ankles and knees were, therefore, more than of fleeting discomfort at such times.

One other point: the joint symptoms came earlier than the so-called pneumonia — that is, before he had been given sulfonamides.

In regard to Dr. Beckman's question about the reason for taking the gastrointestinal series — it was ordered primarily because the patient had considerable nausea and vomiting, but also because we were trying to think of every possible lead. To our great surprise we found a local lesion. There was very little in the history to suggest this. When I saw him originally the possibility of some allergic manifestation was considered, such as angioneurotic edema. It soon seemed obvious, however, that an allergic mechanism was unlikely but that if present at all, it must have been of the delayed reaction type, which one thinks of in connection with periarteritis nodosa. There was little evidence for chronic arthritis. Periarteritis nodosa seemed the most likely diagnosis but one made with only modified enthusiasm.

Dr. John W. Cass: During the past four or five years I saw him once in a while when his family physician was away. He asked me first to see him because he was acutely ill and had a temperature of 104°F. He complained bitterly of pain in the joints, although it was not possible to see anything abnormal about the joints. He could not move them without excruciating pain. This quieted down. He said it was like all the attacks except that there was no swelling. I asked him to call me if he had swelling again. Two years later he called and said that he had another attack with swelling. He had definite swelling of the hands, but more like urticaria than joint swelling. I did not see him again until he became very ill. I thought the patient had some type of atypical rheumatoid arthritis, and I referred him to Dr. Burrage because the one time that I had seen him in an attack of joint pain and swelling I thought that it resembled angioneurotic edema. The urine was examined several times, and it was apparent from that time on that he had progressive signs of kidney disease. The albuminuria increased, there were more casts, and the amount of urine was definitely less. The terminal picture was one of wasting disease with definite signs of kidney disease. He definitely had atrophy of the muscles. There was no question about it. It may have been atrophy of disuse, but at the same time it was far out of proportion to what one would expect. I saw him within an hour of his death and did not realize that he was going to die so soon. I expected him to die in clear-cut uremia, but he was not drowsy. The only thing that I was clear about was that he had a terminal stage of some generalized disease. At first the picture seemed like rheumatoid arthritis; terminally, it was more in keeping with periarteritis nodosa.

Clinical Diagnoses

Fever of unknown etiology.
Periarteritis nodosa.

Dr. Beckman's Diagnoses

Periarteritis nodosa.
Gallstone.

Anatomical Diagnoses

Diffuse myeloma of the bone marrow.
Amyloidosis of liver, spleen and kidneys.
Superimposed Bence–Jones proteinuria, kidney?
Gastric ulcer, healed.
Cholelithiasis.
Hemorrhagic enteritis.
Arteriosclerosis, generalized, moderate.

Pathological Discussion

Dr. Mallory: The autopsy on this man showed an enlarged liver and spleen and very greatly enlarged kidneys. The liver was very pale and firm and slightly waxy in character. The spleen presented visible granulations in the region of the corpuscles. The gross appearance was so characteristic of amyloid disease that an iodine reaction was done at the time of autopsy and was strongly positive. The gastric lesion appeared to be an old, partially healed, benign, peptic ulcer very close to the pylorus. At the time of autopsy we found nothing that would explain the existence of amyloidosis in this patient.

When the microscopical sections came through it was obvious that the majority of the bone marrow was replaced by immature cells only faintly resembling plasma cells but, nevertheless, within the limits of what we see in certain cases of multiple myeloma. Sometimes very severe amyloidosis does occur in association with myeloma, and I believe that is the histologic background in this case. The kidneys were very remarkable in that they showed only mild amyloid deposits but the most severe hyaline degeneration in the convoluted tubules that I have ever seen. There were also very numerous casts in some of the lower tubules. I did not pay much attention to them at first, but one of the pathologists, not knowing the history of the case, asked me if the man had a myeloma so there may also have been a Bence–Jones element in these kidneys as well as amyloidosis. The urine was never examined for Bence–Jones protein so that we are unable to determine that.

CASE 35042

Presentation of Case

A seventy-four-year-old egg tester was admitted to the hospital because of vomiting of four days' duration.

He had been well and working up until about three months before entry, when he suddenly developed nausea, vomiting and generalized cramping pain. He also noted diarrhea, the stools being brown, liquid and not bloody. He was admitted to another hospital, where physical examination revealed a semicomatose man in acute abdominal pain. The skin was cold and clammy. The abdomen was slightly distended, tender and tympanitic, and no peristaltic sounds were heard. The prostate was slightly enlarged. The blood pressure was 158 systolic, 70 diastolic. The temperature was 100°F. (rectally). The urine had a specific gravity of 1.012 and gave a ++ test for albumin, and the sediment contained 0-2 white cells and 2-4 red cells per high-power field and + bacteria. The red-cell count was 3,970,000, with a hemoglobin of 11.7 gm., and the white-cell count 7750, with 63 per cent neutrophils. The blood sugar was 135 mg. per 100 cc., the nonprotein nitrogen 136 mg. per 100 cc., the carbon dioxide 32.5 milliequiv. per liter and the amylase 64 units. A guaiac test of the stool was +++. A roentgenogram showed gas in the stomach and left colon. The kidneys were well outlined and normal in size, shape and position. The cecum and transverse and ascending colon were distended by gas, and barium flowed freely through the splenic flexure. The patient was unco-operative, and the examination was unsatisfactory. Three days later an upper gastrointestinal series revealed no abnormality in the esophagus, stomach or small bowel. A six-hour film showed the terminal ileum, cecum, transverse colon, descending colon and sigmoid partially outlined by barium. He was placed on Miller–Abbott tube for distention and given intravenous fluids, streptomycin and penicillin. Agglutination tests for typhoid O and H antigens, paratyphoid A and B and Proteus OX-19 were reported as negative. Stool culture showed no enteric pathogens. Repeated blood cultures were negative. After three days of therapy the nonprotein nitrogen was 162 mg., total protein 4.7 gm. per 100 cc., phosphorus 5.5 mg. per 100 cc. and uric acid 11.8 mg. per 100 cc. The diarrhea continued unabated. Intravenous fluids were continued but stopped on the twentieth hospital day. The temperature had fluctuated throughout the hospital stay between 99 and 101°F., rectally. The diarrhea began to come under control, and fluids were given more and more by mouth. The stool guaiac tests became negative, and on the eighteenth hospital day the nonprotein nitrogen had fallen to 32 mg. per 100 cc. and the carbon dioxide combining power had risen to 43 vol. per cent. The urine specific gravity throughout the hospital stay remained fixed between 1.007 and 1.013. There had been continuous microscopical pyuria, the sediment averaging 15 to 25 white blood cells per high-power field. He remained very weak, and in view of what was considered to be the chronic nature of his disease, it was recommended that further care be continued in a chronic-disease hospital. He was

discharged to a convalescent home, where he remained two weeks.

In the interval, some seven weeks before admission to this hospital, the patient felt well with no specific complaints. Four days before entry he became confused and incontinent of urine. On the following day he began vomiting, became increasingly weak, and for forty-eight hours before admission had been unable to retain anything by mouth. The vomitus was occasionally "green bile" and never contained blood or coffee-grounds material. The bowels had moved regularly. There was some right abdominal and left chest pain.

Twenty-five years previously he was operated on for a "twisted bowel," which was "untwisted at the time of operation." For six years prior to admission he had noted episodes of diarrhea occurring every three or four months. For five years before admission he experienced urinary incontinence and nocturia. His normal weight had been 210 pounds, and a daughter stated that he had been losing weight progressively.

Physical examination revealed a somewhat disoriented, pale, dehydrated, elderly man in no acute distress. He regurgitated a green fluid regularly. The chest was clear; the diaphragm was high. There were dullness and decreased breath sounds and vocal fremitus at the right base, with egophony above. The heart was not enlarged to percussion. The abdomen was mildly distended and tympanitic throughout. Peristalsis was decreased but of normal pitch. There was some tenderness on the left but no rebound tenderness. There were no rectal masses. The prostate was somewhat enlarged. The legs and sacrum showed a + edema.

The temperature was 98.6°F., the pulse 94, and the respirations 24. The blood pressure was 90 systolic, 60 diastolic.

The urine had a specific gravity of 1.012 and gave a + test for albumin, and the sediment contained 4-5 white blood cells and a rare red blood cell and hyaline cast per high-power field. The red-cell count was 3,500,000, with a hemoglobin of 13 gm., and the white-cell count was 15,100, with 94 per cent neutrophils. The blood nonprotein nitrogen was 48 mg. and the total protein 4.8 gm. per 100 cc., the chloride 102 milliequiv. and the sodium 143.9 milliequiv. per liter, and the blood sugar 104 mg. per 100 cc. A stool gave a + guaiac reaction. On the following day the nonprotein nitrogen was 56 mg. and the total protein 4.5 gm. per 100 cc., the chloride 94 milliequiv. the carbon dioxide 28.1 milliequiv., the sodium 141.7 and the potassium 3.8 milliequiv. per liter. A culture of the bladder washings grew abundant gram-negative cocci and colon bacilli.

In the hospital the patient was kept on intestinal suction and intravenous fluids. He became oliguric, the urine output being 100 cc. in the first twenty-four hours after admission. He remained disoriented. A roentgenogram of the abdomen on the day of admission showed the Harris tube in the stomach. The colon was filled with gas and fecal material but was not definitely dilated. Gas and fecal material were present in the rectum. There were dilated, air-filled loops of small bowel. A roentgenogram of the chest showed homogeneous ground-glass density on the right and patches of increased density on the left. On the second hospital day the white-cell count rose to 25,000, with 98 per cent neutrophils. The urine contained many white blood cells. The temperature was 99°F. On the third hospital day his outward appearance was about the same. He was still confused. The abdomen appeared to be a little more distended. Peristalsis was absent. There were more resistance and tenderness in the lower quadrants. The temperature rose as high as 100°F., and the pulse and respirations remained at 120 and 24, respectively. The urine output was negligible. The white-cell count was 22,500, with 98 per cent neutrophils. Twenty-four hours later the temperature was 99.4°F., the pulse 115, and the respirations as high as 28. The blood pressure was 70 systolic, 40 diastolic. The urine output during the previous day had been less than 50 cc. The nonprotein nitrogen was 90 mg. per 100 cc., and the chloride 93 and the carbon dioxide 25 milliequiv. per liter. On the following day the patient was semicomatose, with a uremic odor. On the following morning he died.

Differential Diagnosis

Dr. Daniel S. Ellis: It seems to me that the object of this case is primarily to state whether or not this patient had some intra-abdominal disease in addition to renal disease, which is quite apparent. At the time of the first admission because of abdominal pain, nausea and vomiting he was found to have definite evidence of renal disease and uremia, and in the subsequent course of events he was treated with antibiotics and paren-

teral fluids. The gastrointestinal symptoms disappeared, the urinary function returned to approximately normal, and he was discharged. It is unfortunate that this admission was at another hospital because we do not have the x-ray films. Therefore, we have to take at face value the statement that no gastrointestinal-tract disease was demonstrated by the various barium examinations done at the time of this illness.

There are several things that make me wonder a little as far as the abdominal pain, nausea and vomiting and diarrhea are concerned. In the absence of any demonstrated abnormal signs, either on physical examination or x-ray examination of gastrointestinal tract or abdomen, I am forced to believe that the gastrointestinal symptoms were on the basis of uremia. It is well known that patients with uremia may have abdominal pain, diarrhea and an ulcerative process involving the entire gastrointestinal tract. The only thing that makes me hesitate a little bit is the amylase report of 64 units. This is high in our laboratory. This is only one report, and I think that I will merely mention it as being abnormal. This man could have had pancreatitis. The low white-cell count is a little bit against it. The fact that examination later showed a leukocytosis makes me think that if he had had a real pancreatitis or intra-abdominal infection at the time of the first admission, it would have been evidenced by an elevation of the white-cell count, which was not observed. I believe that he was uremic, that he was moderately acidotic, and that he was having diarrhea and bloody stools on the basis of renal disease. This theory is further supported by the fact that when treated with supportive measures tending to rehydration to stimulation of urinary output and to control of infection, he improved, and his abdominal symptoms subsided. At the time of discharge he was not having diarrhea, pain, nausea or vomiting; the nonprotein nitrogen was normal but he still had white cells in the urine.

The second episode of illness, as much as I have studied it and tried to arrive at a decision, I am unable to make anything more of than an exacerbation of renal disease in an elderly man, with renewed renal failure and uremia. This time he did not have as much diarrhea. He did have a markedly increased leukocytosis and at this time had a positive urine culture. I would like, if possible, Dr. Wyman, to see any films that you may have to be sure again that some trouble in the abdomen was not developing and to make sure that he did not have pneumonia.

Dr. Stanley M. Wyman: These portable films taken on a very sick patient are of poor quality. They show hazy, homogeneous density in the right chest laterally, which obscures the right leaf of the diaphragm and appears quite consistent with fluid. The right lung shows, as far as I can see, no definite intrinsic disease, and I am unable to see any active process going on in the left lung. The film of the abdomen shows, as reported, gas in nondilated loops of large and small bowel down to the rectum. I do not see any unusual masses or any abnormal calcification except in the prostate.

Dr. Ellis: Would you say there was any difference between the distention in the large or the small bowel? Is there any point of obstruction that you can see?

Dr. Wyman: No; I cannot make a diagnosis of either large-bowel or small-bowel obstruction.

Dr. Ellis: This patient is said to have been operated on once for volvulus of the intestinal tract. It is reported that this was untwisted at the time. At the present admission he had nausea and vomiting, the vomitus containing bile, so that he was regurgitating small-bowel contents. Certainly I could not exclude the possibility that he had an intestinal obstruction. On the other hand, I do not believe this to be true. I believe that the distention seen in the x-ray film is that of a critically ill, elderly man, and the gas-filled loops are probably those of ileus and loss of tone rather than obstruction. The vomiting also, I think, goes with the renal disease. I am going to say that all the symptoms are on the basis of renal disease.

The problem is, What kind of renal disease or urinary-tract disease did this man have? I cannot get away from the definite evidence of an infection, which was manifested by the large number of white cells, positive urine culture and a white-cell count going as high as 22,500. So I believe that we are probably dealing with chronic pyelonephritis rather than a chronic glomerulonephritis. The fall in blood pressure throughout the illness, I think, was probably not due to any acute coronary insufficiency but to a debilitating illness, gradually progressing, in an acutely toxic, critically ill man, who probably had some pneumonia and atelectasis, but I do not

believe we can say that he had lobar pneumonia. The fluid in the chest and the pitting edema can be explained by a combination of things — for example, the low serum protein, uremia and renal disease.

My final diagnosis, without "hemming and hawing" any more, is that the patient had chronic pyelonephritis with uremia. He had some terminal atelectasis or bronchopneumonia and a right hydrothorax, and I have insufficient evidence to go any farther. I do not believe that he had any intra-abdominal disease. As already mentioned from the record there is a possibility of pancreatitis, and possibly he had had volvulus of the small bowel with obstruction to account for the nausea and vomiting, but I would question that. I cannot make a diagnosis of intra-abdominal disease on the history as given.

Dr. Donald S. King: I had an advantage over Dr. Ellis because I saw this patient while he was alive and I had a chance to examine his abdomen. In fact, the day before he died I sat down with his problem and put my conclusion in the record. However, I did not do well. We were confused at first because he seemed to be having exactly the same symptoms when we saw him as he had had in the other hospital. He was discharged from that hospital with a diagnosis of uremic gastroenteritis, and he seemed to get along perfectly well on that diagnosis until he was admitted to our wards. Our first impression was that he again had uremia with gastroenteritis, and this diagnosis was sustained in part by the oliguria. But when we found that his nonprot ein nitrogen was around 50 mg. per 100 cc., we began to doubt whether uremia would explain all the findings. We were particularly disturbed when his white-cell count began to rise. But I never realized how serious his abdominal condition was, and I thought that he might have a mesenteric thrombosis.

Dr. Ellis: There is no detailed report of the examination of the abdomen, which might be fairly important. It just says that there was resistance and tenderness in the lower quadrant. Did he have real spasm and tenderness? If so, was it in the region of the bladder and the lower ureter?

Dr. King: There was no marked tenderness or spasm that I can recall. Is Dr. Littlefield here? He knows more about that.

Dr. John W. Littlefield: I agree to that. The initial surgical examination will describe it, I think.

Dr. King: The record states that on examination the patient was pale, slightly disoriented and acutely ill. The abdomen was full and soft, and then the record says "tender" — but does not state where — without masses and with absent peristalsis. At that time the surgeon thought that uremia would be a satisfactory diagnosis.

Dr. Ellis: Was the patient ever sigmoidoscoped?

Dr. King: I think he was not. He was a very sick man.

Dr. Ellis: It is obvious that he had an ulcerative process going on in the intestinal tract. I think that there are any number of possibilities if he did not have what I have previously said I think he had. But on the basis of the record I have to leave it there.

Dr. Tracy B. Mallory: I would like to ask if the clinicians remember any patient with uremic enteritis who recovered from the episode.

Dr. Marian Ropes: I cannot remember having seen it.

Dr. Mallory: It is a fairly common condition immediately before death, and I do not know whether the patient ever recovers from it or not.

Dr. King: The discharge diagnoses from the other hospital were chronic nephritis, uremia, uremic gastroenteritis and benign prostatic hypertrophy.

Dr. Ellis: I should like to ask Dr. Ropes if the uric acid of 11.8 mg. per 100 cc. is of any significance.

Dr. Ropes: At the time he had evidence of so much retention that I think it means nothing.

Clinical Diagnoses

Chronic nephritis, with uremia.
Intestinal obstruction of undetermined cause.

Dr. Ellis's Diagnoses

Chronic pyelonephritis.
Chronic glomerulonephritis?
Uremia.
Right hydrothorax.
Bronchial pneumonia — atelectasis.
Generalized arteriosclerosis.
Benign prostatic hypertrophy.

Anatomical Diagnoses

Carcinoma of colon, with probable perforation.
Generalized peritonitis.
Nephrosclerosis.
Cholecystitis and cholelithiasis.
Anasarca.
Benign prostatic hypertrophy.
Operative wound, old: posterior gastroenterostomy.

Pathological Discussion

Dr. Mallory: The autopsy on this patient, I am sure, was a complete surprise to everyone. The major lesion was a cancer of the bowel located at the splenic flexure. This was about 4 cm. long, completely encircling the bowel, which was very deeply ulcerated. There was a generalized fibrinopurulent peritonitis of sufficient age so that it had become separated into a great many pus-filled cavities, separated from one another by fibrinous adhesions. Actual perforation of the bowel could not be demonstrated with a probe at the time of autopsy, but since one of the larger intra-abdominal abscesses was in the immediate neighborhood of the lesion, I have no doubt that it had perforated and was the source of the peritonitis.

The lungs showed very marked congestion, atelectasis and edema but no pneumonia. There was pleural effusion of 900 cc. on the right side. The kidneys weighed just over 300 gm., had a slightly narrowed cortex and microscopically showed a severe degree of arteriolar narrowing and hyalinization — the type of kidney one would expect to see with a benign hypertension. The process did not look far enough advanced to have in itself been the cause of the uremia, although to try and guess from the appearance of such a kidney whether or not the patient had uremia is very dangerous, of course.

The former operation, described only as an operation for twisted bowel, had been a gastroenterostomy. We found nothing to explain why that had been done. The gastroenterostomy was patent. Our opinion was that the patient had a moderate grade of vascular nephritis, which probably alone would not have produced uremia but did so in association with peritonitis, and the dehydration that would go with that. A considerable degree of nitrogen retention is a common phenomenon in general peritonitis.

Dr. Ellis: Did he have the peritonitis when he was admitted to the first hospital?

Dr. Mallory: I cannot say whether or not he had some degree of peritonitis in the upper abdomen the first time. He had some old, fibrous adhesions, which were most extensive in the region of the previous operative scar. I do not believe I can say whether some of them were produced by an attack of localized peritonitis weeks before at the time of the first illness. They may have traced way back to the orginal disease twenty-five years previously.

Dr. Ellis: It is quite possible that peritonitis was at first controlled by the streptomycin and penicillin. After these were stopped it flared up again in more chronic, localized form. It certainly is true that we often see kidneys that are borderline and then tipped into failure by any acute process. I think it possible in view of the findings to explain the uremia on that basis. It seems strange that the peritonitis was not more manifest clinically.

Dr. King: We thought so too.

Dr. Mallory: The paralytic ileus was the only evidence positively in favor of it

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BUDGET FOR 1949

As the country enters into that period of the year immediately following the winter solstice when it wrestles, individually and collectively, with its fiscal problems, some thought must also be given to the pecuniary affairs of the Massachusetts Medical Society. These affairs, as the Treasurer will bear witness, have grown; shortly the Council will vote upon the largest budget in the history of the Society.

None of the items in this budget need cause concern, for the Society is solidly solvent; all of them require the scrutiny of the councilors, who should have a clear conception of the magnitude of the works that they are directing and their importance.

The largest single item in this budget is the $27,000 that goes to the support of the Boston Medical Library, and represents one of the important reasons for the increase in the Society's membership assessment in 1948. For the five dollars of his assessment that is so allocated, each fellow of the Society receives membership in the Library and, perhaps more important, the consciousness that he is contributing a modest share toward the support of a basic factor in medical education and in intellectual improvement in his profession. This support must be reaffirmed so long as it is needed, as one of the soberest and most mature commitments that a physician can make.

Other items in the Society's budget are concrete evidence of the fact that the relation of physicians to the public have changed; that they have become more complex and that they are subject to pressures that call for constant strengthening from within. The payroll has justifiably increased as headquarters duties have become more numerous and more exacting. The expenses of the officers and committees in discharging their functions have increased, a considerable share of this increase being charged to public relations, including the expenses of the Committee on Legislation; the refund to the district societies was increased last year from $4000 to $8000; the employees' pension plan adds $4000 yearly; the Council has voted $10,000 annually to the Medical Benevolent Society.

The sum of $10,000 has again been allocated to the *Journal* as the only commitment that the Society is presently asked to make for over 6000 subscriptions and the publication of the Proceedings; in four years $5000 only of this appropriation has been retained for the use of the *Journal*.

The budget requested for 1949 is $142,155, the income of the Society being probably over $150,000. The margin is safe, but it must in the future as at present be carefully guarded.

SWORDS AND PLOUGHSHARES

How can health and medical-care standards of American soldiers and airmen be kept at their present level, the highest of any army in the world today? The Army Advisory Committee* asks the

*To save — not to destroy. *Bull. Army Advisory Committee* 2:1, October, 1948.

question, one answer to which may be found in the Medical Department's plan for peace-time operation of Reserve Officers Training Corps units in the approved medical schools of the United States. An account of the work of these units within the framework of the undergraduate medical curriculum is given elsewhere in this issue of the *Journal*. To those whose recollections of medical ROTC are strongly colored by past experience of litter bearing and close-order drill, unmistakable signs of progress will be revealed.

ROTC units now installed are designed to obtain a total enrollment of 8000 for all four classes in medical schools, and to produce annually about 2000 first lieutenants. In the year 1946-1947, 20 units were in operation; in 1947-1948, 23 units were added; and in 1948-1949 there are an additional 6, bringing to 49 the total units now operating. Within a period of three years this has therefore become a universal feature of medical education in the United States. On a similar elective basis the Army has established 18 units in the dental schools, 6 in the veterinary schools, and 4 in the schools of pharmacy.

The purpose of the medical ROTC is to develop a body of Reserve Medical Corps officers who will be capable of performing professional duties and also of taking care of themselves within the structure of the Army, and without further training on mobilization day — or at any time when they may be called to active service. A secondary mission of the plan is that of acquainting the medical student with the facts concerning a career in the Army Medical Department, with the further possibility that he will become interested in obtaining an Army internship and in applying for a regular commission.

All this is preparedness in the best sense: preparedness to save — not to destroy; to conserve — not to dissipate. It is preventive medicine, organized on a scale and basis heretofore unknown.

A MEETING OF MINDS

PHYSICIANS are making up their minds about the future of the broad field of psychiatry, as evidenced by the International Congress on Mental Health, held in London in August, 1948. Two thousand men and women, representing fifty-five countries, at that time discussed mental health and formulated specific plans for its betterment throughout the world. Although the largest number of participants were psychiatrists, the preliminary study groups were made up not only of physicians but also of psychologists, sociologists, anthropologists, educators, theologists and representatives of relevant disciplines.

The purpose of the Congress was threefold: to bring together psychiatrists from all the world, that they might secure an over-all picture of the psychiatric needs of human beings and formulate methods of solving these problems; to study the psychologic causes of war and the part physicians may play in prevention; and to form an international organization to engage actively in promoting mental health in every nation.

Representatives from fifty-five countries participated in the incorporation of this organization, with offices in Geneva. Membership is made up of professional societies in the related disciplines concerned with mental health as well as of the mental-hygiene societies in each participating country. These member associations will send representatives to the annual meeting of the Mental Health Assembly. It is expected that the work of the World Federation for Mental Health will be incorporated with the World Health Organization and the whole correlated with the United Nations Organization, the World Federation offering a means for transnational collaboration on the problems of mental health.

There can be no question that this is a most important development in the field of medicine and one in which physicians will be interested and in which they will want to participate, for mental illness is probably the greatest single cause of suffering throughout the world, and it is to physicians that people must turn for individual treatment, guidance and public-health measures directed toward its prevention. For the first time in history these facts are now generally recognized, and the organization that has been perfected deserves support. To this end physicians are increasing their knowledge of the physiologic, psychologic and sociologic factors relating to mental health, that they may be better prepared to treat patients, formulate mental-

hygiene principles and implement measures for the improvement of mental health.

Plans have been completed for the President of the United States to proclaim a Mental Health Week in April, 1949. This will be followed by proclamations from the governors of the forty-eight states and wide publicity through press and radio. There will be active co-operation from medical societies and other organizations directed toward the betterment of mental-health conditions in this country. In all this the medical profession will assume the leadership that it has always shown in matters pertaining to individual and public health.

PIED PIPERS OF MADISON

CURRENT researches in the department of zoology of the University of Wisconsin on the habits of rodents are beginning to reveal interesting facts concerning the life and manners of these small inhabitants of the underworld. As a result it is believed that a careful study of the life habits and population cycles of rats, bats, mice and muskrats may lead to improved methods of rodent control.

Five College of Agriculture animal buildings, infested with wild mice, comprise the location of the study; here eager scientists, employing the reverse process of belling the cat, are catching and marking the diminutive enemies of the new look.

A number of facts have already been elicited. Mice, when living in peace and comfort, rarely range more than 30 or 40 feet from home, and rats seldom farther than 100 feet from the food supply. Since the rate of reproduction averages 30 young per year per female with about 5 survivors, overpopulation soon becomes a factor, however, with competition and outbreaks of civil war resulting, as with human beings. Perhaps from this analogy the frequently quoted question may arise: "Are we men or are we mice?"

Various methods of rodent control have been tested and evaluated. The best of these is prevention, and to discourage the rodent population this implies cutting off the food supply. Entry holes must be plugged, garbage removed, refuges cleaned and cupboards either mouseproofed or kept as bare as Mother Hubbard's. Rats abandoning their native locality for any reason are never welcomed into another colony.

In the frontal attack poisoning is the least effective weapon, a good hunting cat one of the best. The old-fashioned snap-trap remains a steadily effective mouse-eliminator. Not mentioned as participating in the Wisconsin field trials is a new and remarkable gadget for the mass liquidation of domestic rodents. This machine, equipped with an electric eye, is set up adjacent to a rat runway. When a victim crosses the beam he is quietly seized by the neck, electrocuted and tossed aside, after which this supreme effort of the electrocutioner's art promptly resets itself.

The rodent population so far is nearly holding its own, but to do so it must live dangerously.

Fourth-year students in approved medical schools are reminded of the *Journal's* prize essay competition on preventive medicine.

For further information see *The New England Journal of Medicine*, September 30, 1948, p. 525, or write to the editor.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

ABBE — Alanson J. Abbe, M.D., formerly of Fall River, died on January 3. He was in his eighty-eighth year.

Dr. Abbe received his degree from Harvard Medical School in 1885. He was formerly secretary-treasurer of Bristol South District Medical Society and ophthalmic surgeon at Union Hospital, Fall River.

A son, a daughter and two grandchildren survive.

CHENERY — William E. Chenery, M.D., of Brookline, died on January 3. He was in his eighty-fifth year.

Dr. Chenery received his degree from Harvard Medical School in 1890. He was formerly surgeon at St. Elizabeth's Hospital, consultant at Boston Dispensary, New England Deaconess and Evangeline Booth hospitals and a member of the staff of New England Baptist Hospital. He was a member of the American Academy of Ophthalmology and Oto-Laryngology, American Laryngological and Rhinological and Otological Society and a fellow of the American College of Surgeons and American Medical Association.

His widow and a niece survive.

GOLDBERG — Samuel B. Goldberg, M.D., of Medford, died on January 5. He was in his forty-sixth year.

Dr. Goldberg received his degree from Middlesex University School of Medicine in 1928.

His widow, a son, a daughter, three brothers and a sister survive.

NEW HAMPSHIRE MEDICAL SOCIETY

DEATH

STICKNEY — Henry L. Stickney, M.D., formerly of Manchester, died on December 17. He was in his seventy-eighth year.

Dr. Stickney received his degree from University of Vermont College of Medicine in 1894. He had served in various Veterans Administration hospitals and at one time owned and operated the Hillcrest Hospital in Manchester. He was formerly a member of the staff of the Mayo Clinic, Rochester, Minnesota, and was a fellow of the American Medical Association.

His widow, two sons, a daughter, a brother, eight grandchildren and a great-grandchild survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR DECEMBER, 1948

RÉSUMÉ

DISEASE	DECEMBER 1948	DECEMBER 1947	SEVEN-YEAR MEDIAN
Chancroid	3	6	3*
Chicken pox	3022	1680	1444
Diphtheria	47	36	29
Dog bite	668	616	517
Dysentery, bacillary	2	19	12
German measles	83	64	68
Gonorrhea	257	262	316
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	1	2	1*
Malaria	0	7	*7
Measles	4674	459	702
Meningitis, meningococcal	8	2	12
Meningitis, Pfeiffer-bacillus	5	8	3
Meningitis, pneumococcal	7	3	6†
Meningitis, staphylococcal	1	0	0†
Meningitis, streptococcal	0	0	0†
Meningitis, undetermined	6	4	3†
Mumps	1319	1267	1080
Pneumonia, lobar	140	96	208
Poliomyelitis	2	8	11
Salmonellosis	4	9	5
Scarlet fever	699	475	978
Syphilis	180	274	373
Tuberculosis, pulmonary	217	210	207
Tuberculosis, other forms	16	14	13
Typhoid fever	2	4	4
Undulant fever	1	4	3
Whooping cough	331	682	682

*Four-year median.
†Six-year median.

COMMENT

Diseases above the seven-year median were chicken pox, diphtheria, German measles and mumps.

Diseases below the seven-year median were bacillary dysentery, lobar pneumonia, poliomyelitis, scarlet fever, typhoid fever, undulant fever and whooping cough.

Diphtheria was still too prevalent. For ten consecutive years, 1936–1946, the incidence was lower than that during December. A total of 139 cases was reported during the last four months of 1948, compared to 85 cases in the same period in 1947.

The incidence of chicken pox was the highest ever reported for December, and that for measles was the highest since 1925. The frequency of mumps, which was still higher than the seven-year median, seems to be declining.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from: Arlington, 3; Blackstone, 1; Boston, 23; Bridgewater, 1; Brookline, 1; Chelsea, 2; Danvers, 2; Everett, 2; Haverhill, 1; Lowell, 1; Nahant, 4; Revere, 1; Salem, 1; Somerville, 1; Springfield, 1; Waltham, 1; Winchester, 1; total, 47.

Dysentery, amebic, was reported from: Boston, 1; total, 1.

Dysentery, bacillary, was reported from: Boston, 1; Worcester, 1; total, 2.

Encephalitis, infectious, was reported from: Andover, 1; Malden, 1; Westfield, 1; Worcester, 1; total, 4.

Lymphocytic choriomeningitis was reported from: Winthrop, 1; total, 1.

Meningitis, meningococcal, was reported from: Boston, 1; Harwich, 1; New Bedford, 1; Pittsfield, 1; Somerville, 2; Williamstown, 1; Winthrop, 1; total, 8.

Meningitis, Pfeiffer-bacillus, was reported from: Malden, 1; Southbridge, 1; Springfield, 3; total, 5.

Meningitis, pneumococcal, was reported from: Braintree, 1; Chesterfield, 1; Gloucester, 1; Medford, 1; Somerville, 1; West Springfield, 1; Weston, 1; total, 7.

Meningitis, staphylococcal, was reported from: Chicopee, 1; total, 1.

Meningitis, undetermined, was reported from: Adams, 1; Avon, 1; East Brookfield, 1; Milton, 1; West Boylston, 1; Worcester, 1; total, 6.

Poliomyelitis was reported from: Hardwick, 1; West Springfield, 1; total, 2.

Salmonellosis was reported from: Boston, 2; Lynn, 1; Winchester, 1; total, 4.

Septic sore throat was reported from: Boston, 4; Medford, 2; total, 6.

Tetanus was reported from: Lawrence, 1; total, 1.

Trichinosis was reported from: Boston, 1; total, 1.

Tularemia was reported from: Sandwich, 1; total, 1.

Typhoid fever was reported from: Boston, 1; Swansea, 1; total, 2.

Undulant fever was reported from: Grafton, 1; total, 1.

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The December schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows:

CLINIC	DATE	CLINIC CONSULTANT
Haverhill	February 2	William T. Green
Lowell	February 4	Albert H. Brewster
Salem	February 7	Paul W. Hugenberger
Gardner	February 8	Carter R. Rowe
Brockton	February 10	George W. Van Gorder
Worcester	February 11	John W. O'Meara
Greenfield	February 14	Charles L. Sturdevant
Springfield	February 15	Garry deN. Hough, Jr.
Pittsfield	February 16	Frank A. Slowick
Hyannis	February 24	Paul L. Norton
Fall River	February 28	David S. Grice

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

MISCELLANY

PRESIDENT OF THE AMERICAN ACADEMY OF PEDIATRICS

Dr. Warren R. Sisson, of Boston, having served for a year as president-elect of the American Academy of Pediatrics, has assumed the office of president. Dr. Sisson, a graduate of Johns Hopkins University School of Medicine and formerly a member of the Department of Pediatrics of Harvard Medical School, served also as chairman of the committee for the Study of Child Health Service of the Academy.

CORRESPONDENCE

STATISTICS OF PNEUMONIA

To the Editor: The editorial "Influenza and Pneumonia" in the December 9 issue of the *Journal* is timely and appropriate, but by implication it perpetuates an error when it states "A most significant downward trend in the figures began in the early 1930's, when specific serum treatment for many types of pneumonia was introduced." The figures for Massachusetts, where an intensive serum program was conducted in the 1930's, do not show any downward trend in that decade until 1938, after the use of chemotherapy became widespread. As a matter of fact the Massachusetts figure for 1936 (96.3) is higher than that for 1930 (95.0), and back in 1927 it had dipped to 97.5.

All that we are ever likely to know about the serum treatment of pneumonia is now recorded. It is too bad to let these legends continue; as a profession we do not need to be flattered and do not wish to be falsely recorded by such implications in the history of medicine. I am convinced that a careful study of pneumonia between 1920 and 1937 will fail to reveal any one circumstance that satisfactorily explains the reduction of mortality; it is extremely doubtful that our bedside practices had anything to do with it. Personally I was never convinced that the serums we used in the 1930's were any more effective than those available for the more common types in 1920. Certainly, we have no evidence that any of them compare with the chemical and biologic agents of the past decade.

DWIGHT O'HARA, M.D.

Waltham, Massachusetts

NOTE: A previous editorial, entitled "Pneumococcal Pneumonia," which appeared in the April 17, 1947, issue of the *Journal*, had already taken cognizance of the facts that Dr. O'Hara's letter re-emphasizes. The reference to the figures quoted in the recent editorial was for industrial policyholders from the country as a whole as compiled by the statisticians of the Metropolitan Life Insurance Company. In these figures the temporal if not the causal relation of the drop in pneumonia mortality to the use of serums was implied. The beneficial effects of antipneumococcal serums, particularly those prepared in rabbits and available just prior to the introduction of effective sulfonamides, now constitute only a matter of historical interest. It should be pointed out, however, that much firmer convictions are held by most of those with considerable and intimate experience with the use of serums in large numbers of cases. Regarding the effects on the mortality statistics for Massachusetts, too many factors are involved in the compilations of such figures to warrant any serious interpretations, controversies or comparisons with carefully studied clinical material compiled by competent observers. — ED.

A CORRECTION

To the Editor: I appreciate very much the honor of the editorial comment in the December 9 issue of the *Journal*. I would, however, like to make two minor corrections and add a note.

My college class was 1908; 1911 for my medical class was correct.

The decoration of the Order of the White Lion was given in 1946 to all the members of the American Medical Mission to Czechoslovakia under the auspices of the Unitarian Service Committee in acknowledgment of the helpful work in restoring the medical friendship and co-operation of the two countries. Among those in Boston receiving the decoration were Drs. Joseph Aub, Otto Krayer, Joseph Volker and Joseph Lazansky. At the time of my visit to Prague in April, 1948, I was on my way to another American Medical Mission of the Unitarian Service Committee, this time to Greece and Italy, in which I was associated with ten other doctors, including several more from Boston — namely Drs. Chester Jones, Reidar Sognnaes and Herman DeWilde. I spent a few days in Prague (en route to Athens) to attend the six hundredth anniversary of Charles University, the oldest university in Central Europe, in acknowledgment of the past accomplishments of that great institution. Professor Réné Leriche, of France, and I received honorary doctorates from the faculty of medicine. Other medical candidates were not present, but honorary degrees were bestowed by other faculties on other foreign guests.

In my new role as adviser of the National Heart Institute and executive director of the National Advisory Heart Council I shall continue to reside in New England and to practice medicine half time, following patients whom I have seen in the past. Adjoining my own private office at 264 Beacon Street is a branch office of the National Heart Institute, one of the National Institutes of Health under the United States Public Health Service whose headquarters are at Bethesda, Maryland.

PAUL D. WHITE, M.D.

Boston, Massachusetts

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Practice of Allergy. By Warren T. Vaughan, M.D. Revised by J. Harvey Black, M.D. 4°, cloth, 1132 pp., with 333 illustrations and 81 tables. Second edition. Saint Louis: The C. V. Mosby Company, 1948. $15.00.

This treatise, first published in 1939 by Dr. Vaughan, has been revised for the second edition by Dr. Black, who assumed the authorship after the death of Dr. Vaughan. The text has been revised to bring the subject up to date. The chapters on fungous infection with associated allergy and on vital capacity have been rewritten. A large bibliography follows the text, and a comprehensive index concludes the volume. The type and printing are excellent, but the use of a coated paper makes the volume very heavy. This encyclopedic treatise is recommended for all medical libraries and to all specialists in its field.

Pioneer Life in Kentucky, 1785–1800. By Daniel Drake, M.D. Edited from the original manuscript, with introductory comments and a biographical sketch by Emmet F. Horine, M.D. 8°, cloth, 257 pp., with 8 illustrations and frontispiece. New York: Henry Schuman, 1948. $4.00.

The letters of Dr. Daniel Drake, edited by his son, Charles Daniel Drake, were first published in 1870. The letters were republished in 1907, and both editions have long been out of print. In an examination and comparison of the original letters, now in the library of the Cincinnati General Hospital, with the published letters, Dr. Horine found many discrepancies and omissions. It was found that Dr. Charles Drake took many liberties with his father's letters in an attempt to improve their literary style. In this edition the letters have been faithfully reproduced in Dr. Drake's phraseology from the original manuscript letters. Dr. Daniel Drake was a pioneer western physician, the first medical student of Cincinnati and a professor at Transylvania University at Lexington, Kentucky, in 1817. He was prominent in Ohio affairs, establishing the Medical College of Ohio, the Western Museum, the Cincinnati College and the *Western Journal of the Medical and Physical Sciences*, of which periodical he was editor from 1827 to 1838. This important book should be in all medical and general historical collections.

Treatment of Heart Disease. By William A. Brams, M.S., M.D., Ph.D., associate professor of medicine, Northwestern University Medical School, and attending physician, Michael Reese Hospital, Chicago. 8°, cloth, 195 pp., with 11 illustrations. Philadelphia: W. B. Saunders Company, 1948. $3.50.

This monograph has been written for the general practitioner and medical student as a systematic and practical guide in the treatment of heart disease. It reflects the experience of the author gained in teaching and in private practice and consultation work and does not include methods of treatment used by other heart specialists. The material offered is confined to therapy and does not discuss etiology, symptomatology and diagnosis. A comparatively large amount of space is devoted to congestive heart failure because the author believes that the majority of persons with almost any form of organic heart disease ultimately develop this condition. The first chapter discusses the pharmacologic action of drugs used in treatment, followed by chapters on the various heart diseases. The text is well printed with a good type. The use of a coated paper is not justified by the number of illustrations. A long bibliography concludes the text and there is a good index.

A History of the Heart and the Circulation. By Frederick A. Willius, M.D., M.S. in Med., senior consultant in cardiology, Mayo Clinic, professor of medicine, Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota; and Thomas J. Dry, M.A., M.B., Ch.B., M.S. in Med., consultant, section on cardiology, Mayo

Clinic, associate professor of medicine, Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota. 8°, cloth, 456 pp., with 170 illustrations. Philadelphia: W. B. Saunders Company, 1948. $8.00.

This new history of the heart and circulation is divided into three parts. The first presents a chronologic history from 5000 B.C. to 1925 A.D., arranged by periods. The second consists of twenty special biographies of pioneers in various aspects of the subject, from Hippocrates (c. 460–c. 377 B.C.), to Sir Thomas Lewis (1881–1945). The third is a chronologic presentation according to subjects. To each chapter there is appended an extensive bibliography. Two good indexes of authors and subjects conclude the volume. The text is well written in a seminarrative style and is illustrated with portraits of physicians discussed in the text. The chronologic tables in the third part should prove very valuable for reference purposes. The book should be in all medical-history collections and in all medical libraries, both small and large.

Diagnostic Procedures for Virus and Rickettsial Diseases. Published by The American Public Health Association. 8°, cloth, 352 pp., with 20 illustrations. New York: American Public Health Association, 1948. $4.00.

This book is the joint work of the members of a special committee of the American Public Health Association. Seventeen diseases are discussed by authorities on the various diseases. Laboratory methods applicable to the various diseases are described in the chapters dealing with the diseases. A good index concludes the volume, which is well published. It should be in all medical libraries and medical laboratories.

The Salicylates: A critical bibliographic review. By Martin Gross, M.D., research assistant (assistant professor), Laboratory of Applied Physiology, Yale University School of Medicine; and Leon A. Greenberg, Ph.D., associate professor in applied physiology, Yale University School of Medicine. With an introduction by Howard W. Haggard, M.D., director, Laboratory of Applied Physiology, Yale University School of Medicine. 8°, cloth, 380 pp., with 20 illustrations and 29 tables. New Haven: Hillhouse Press, 1948. $6.00.

This monograph is one of a series projected by the Institute for the Study of Analgesic and Sedative Drugs. The volume on acetanilid was published in 1946. The literature reviewed 4093 titles, and the bibliography uses 173 pages of the book. The first part of the work analyzes and reviews the chemistry, physiology, pharmacology, toxicology and therapeutic uses of the salicylates. The text is well printed with a good type on light paper. An index of subjects concludes the volume. The book is recommended as a reference source for all medical libraries.

The Frightened Child. By Dana Lyon. 8°, cloth, 186 pp. New York: Harper and Brothers, 1948. $2.50.

This novel with a psychologic trend has a physician as one of its characters.

Your Skin and Its Care. By Howard T. Behrman, M.D., and Oscar L. Levin, M.D. 12°, cloth, 255 pp., with 11 illustrations. New York: Emerson Books, Incorporated, 1948. $2.50.

This manual is written for the laity and is devoted to the hygiene of the skin in health and disease, with chapters on the hair, sebaceous glands and quackery in relation to dermatology. The material is well arranged, and the text well written in a simple manner. A glossary of terms concludes the text. There is a good index. The volume is a good example of a popular medical manual.

NOTICES

ANNOUNCEMENT

Dr. Robert R. Commons announces the opening of his office for the practice of internal medicine at 121 North San Vincente Boulevard, Beverly Hills, California.

NEW ENGLAND HEART ASSOCIATION

A meeting of the New England Heart Association will be held in the Auditorium, Boston University School of Medicine, 80 East Concord Street, on Monday, February 14, at 8:15 p.m., Dr. Robert W. Wilkins presiding.

PROGRAM

Observations on Normal and Pathologic Physiology of Postarteriolar Vascular Beds in the Human Forearm and Calf. Drs. J. Litter and R. W. Wilkins.

The Relative Velocity of Plasma and Cells in the Circulation of Man. Drs. C. P. Emerson, E. D. Freis and J. R. Stanton.

Prognosis for Surgically Treated Hypertensive Patients. Dr. R. H. Smithwick.

Comparative Hemodynamic Effects of Small Intravenous Doses of Epinephrine in Normotensive Subjects and in Hypertensive Patients before and after Sympathectomy. Drs. W. E. Judson, C. M. Tinsley and J. W. Culbertson.

A Case of Pheochromocytoma Extensively Studied before and after Surgical Removal. Drs. R. W. Wilkins, W. E. Greer, J. W. Culbertson, C. H. Burnett, M. H. Halperin, J. Litter and R. H. Smithwick.

Interested physicians and medical students are cordially invited to attend.

MASSACHUSETTS MEDICO-LEGAL SOCIETY

The winter meeting of the Massachusetts Medico-Legal Society will be held in the Department of Legal Medicine, Building E-1, Harvard Medical School, on Wednesday, February 9, at 2:30 p.m.

PROGRAM

When to Accept Jurisdiction. Dr. Richard Ford.

The Medical Examiner's View. Dr. Timothy Leary.

Unusual Medicolegal Problems. Dr. Alan R. Moritz.

Establishment of identity and time, cause and manner of death of unknown person twelve years after death.

The benefits of a second autopsy after three years in a wet grave.

Business Meeting.

Refreshments.

HELEN PUTNAM FELLOWSHIP

The Helen Putnam fellowship for advanced research in genetics or mental health, open to women scholars who have their doctorate or who possess equivalent qualifications, will be offered by Radcliffe College for the academic year 1949-1950. The award carries a stipend of $2600 a year with the possibility of renewal.

Applicants are asked to submit a plan of research, and preference will be given to those whose research is already in progress.

Applications should be returned to the Secretary of the Graduate School, Radcliffe College, not later than April 1.

SOCIETY MEETINGS AND CONFERENCES

JANUARY 7–APRIL 13. American College of Surgeons. Sectional Meetings. Page xi, issue of December 23.

FEBRUARY 6. National Conference on Medical Service. Page 80, issue of January 13.

FEBRUARY 9. Massachusetts Medico-Legal Society. Notice above.

FEBRUARY 10. Endoscopy — Its Indications and Limitations. Dr. Edward B. Benedict. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

FEBRUARY 14. New England Heart Association. Notice above.

MARCH 7–9. American Academy of General Practice. Page 728, issue of November 4.

MARCH 28–APRIL 1. American College of Physicians. Page 158, issue of July 22.

MAY 4. New England Obstetrical and Gynecological Society. Springfield Country Club, Springfield.

MAY 16–19. American Urological Association. Biltmore Hotel, Los Angeles, California.

MAY 24–26. Massachusetts Medical Society. Annual Meeting. Worcester Memorial Auditorium, Worcester.

MAY 26–28. American Goiter Association. Hotel Loraine, Madison, Wisconsin.

(Notices concluded on page xiii)